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Health and Environmental Effects Profile for Ethyl Acrylate

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ETHYL ACRYLATE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

The Health and Environmental Effects Profile for Ethyl Acrylate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Ethyl acrylate has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for ethyl acrylate is 4.8×10^{-2} $(mg/kg/day)^{-1}$ for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for ethyl acrylate is 1000.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

Ethyl acrylate is a colorless liquid with an acrid odor (Windholz, 1983). It is soluble in alcohol, ether and chloroform, and is reasonably soluble in water (Weast, 1985; Windholz, 1983). It is a monomer used in the production of a variety of polymers, such as flexible resins for latex paints, textile, paper and leather-finishing resins, and solution polymers for metal finishing and for the production of acrylic fibers (Celanese Chemical Co., 1982; IARC, 1979b). In 1984, three U.S. manufacturers reported production of 306.4 million pounds of ethyl acrylate (USITC, 1985). Currently, four manufacturers at five locations produce this chemical in the United States (SRI, 1986).

Ethyl acrylate is likely to undergo polymerization to an innocuous resin if released to the environment in a spill-type situation (U.S. EPA-NIH, 1986); however, the diluted concentrations, which may be encountered in the environment, are unlikely to polymerize significantly. If released to water, volatilization and indirect photooxidation (by hydroxyl radicals) are expected to be important removal mechanisms. The role of direct photolysis cannot be assessed with the data currently available. Ethyl acrylate has been shown to be significantly biodegradable in two BOD studies (Sasaki, 1978; Price et al., 1974), which suggests that biodegradation in the environment is possible. Adsorption onto sediment, bioconcentration and hydrolysis (except if $pH \geq 9$) are not expected to be important in the aquatic environment. If released to the atmosphere, ethyl acrylate is expected to remain in the vapor-phase and react rapidly with HO radical and ozone, with an estimated half-life of 6.5 hours (U.S. EPA, 1986). If released to soil, ethyl acrylate is expected to be highly mobile based on estimated K_{oc}

values; therefore, significant leaching in soil may occur. Ethyl acrylate may volatilize significantly from soil surfaces. In moist alkaline soils ($pH \geq 9$), hydrolysis is potentially important.

Pertinent ambient air or water monitoring data regarding ethyl acrylate could not be located in the available literature as cited in the Appendix. It is possible that ethyl acrylate will be emitted to the atmosphere or to water from effluents produced during its industrial manufacture or use. Leaching of residual monomer from polymer products, which have been landfilled, may be possible. Ethyl acrylate has been reported to be a volatile component of pineapple concentrate (Näf-Müller and Willhalm, 1971). Polymer products made from ethyl acrylate are permitted for various food contact uses (U.S. EPA, 1977), suggesting that leaching of residual monomer into foods may be possible. Incineration of acrylate polymers may be a source of atmospheric release.

The information concerning toxicity of ethyl acrylate to aquatic biota is very limited. LC_{50} values of 0.74 and 12 mg/ℓ were reported for guppies (Hermens and Leeuwangh, 1982) and brine shrimp (Price et al., 1974), respectively.

Pertinent data regarding the extent and rate of absorption of ethyl acrylate are limited. In rats given a single oral dose of 200 mg/kg ethyl acrylate, there was no parent compound detected in intraocular blood 15-60 minutes post-administration, but there were detectable portal blood levels 15-30 minutes after dosing. These results suggest that ethyl acrylate is absorbed by the gastrointestinal tract.

Stott and McKenna (1984) estimated that 30-70% of an inhaled concentration of ethyl acrylate was absorbed into the bloodstream by the upper respiratory tract of rats. The NTP (1986a) found half-lives of 53-76

minutes in male rats and 66-96 minutes in females for metabolism of ethyl acrylate in individual homogenates of the forestomach, glandular stomach and stomach contents. In vitro blood half-lives were 11.8 and 14.0 minutes for female and male rats, respectively. Nonprotein thiol concentrations were reduced in the isolated stomachs of rats following oral dosing with ethyl acrylate. Rat lung, kidney and liver homogenates hydrolyzed ethyl acrylate to acrylic acid by tissue carboxylesterase (Miller et al., 1981; Silver and Murphy, 1981). In rat blood, however, no acrylic acid was formed, but ethyl acrylate was bound to nonprotein sulfhydryl groups (Miller et al., 1981). Inhibition of carboxylesterase activity in rats increased the conjugation reactions in the lungs, blood, liver and kidneys (Silver and Murphy, 1981). Thus, ethyl acrylate can be hydrolyzed to acrylic acid or conjugated to nonprotein sulfhydryl groups, presumably glutathione, in competitive pathways. Pertinent data regarding the excretion of ethyl acrylate were not located.

An NTP (1986a) report of the potential carcinogenicity of ethyl acrylate after oral (gavage) administration in F344 rats and B6C3F1 mice of both sexes indicated that ethyl acrylate induced squamous cell carcinomas or papillomas (or both) of the forestomach in both species. For both species, dose levels were 0, 100 and 200 mg/kg, 5 days/week for 103 weeks.

No evidence of carcinogenicity was found in rats given up to 2000 ppm in drinking water for 2 years (Borzelleca et al., 1964).

Miller et al. (1985) found no evidence of carcinogenicity in B6C3F1 mice and F344 rats exposed by inhalation to up to 75 ppm (307 mg/m^3) ethyl acrylate, 6 hours/day, 5 days/week, for 27 months, or in rats and mice exposed to 225 ppm (921 mg/m^3), 6 hours/day, 5 days/week for only 6 months, then maintained for 21 months until terminal sacrifice.

DePass et al. (1984) found no increase in epidermal tumor incidence in C3H/Hej male mice skin-painted with 23 mg/mouse ethyl acrylate, 3 times/week for 2 years.

A causal relationship for increased incidences of cancer of the colon and rectum from occupational exposure to ethyl acrylate/methyl methacrylate was suggested in a historic perspective epidemiology study; however, a causal relationship could not be confirmed when further studies at other Rohm and Haas Company plants with less exposure and latency to the same agents were considered (Rohm and Haas Co., 1981, 1984, 1986a,b; Mantel, 1986). Moreover, exposure to ethyl acrylate and methylacrylate could not be separated.

Ethyl acrylate has been found to be nonmutagenic in standard reverse mutation assays with and without metabolic activation (NTP, 1986a; Haworth et al., 1983; Waegemakers and Bensink, 1984). Principally at cytolethal doses, ethyl acrylate was mutagenic to CHL cells (Ishidate et al., 1981) and mouse lymphoma cells (Litton Bionetics, 1984) in culture. Przybojewska et al. (1984) demonstrated genotoxicity of ethyl acrylate in the micronucleus test using Balb/c mice.

Murray et al. (1981) demonstrated that inhalation exposure of rat dams to 50 or 150 ppm (205 or 614 mg/m^3) ethyl acrylate, 6 hours/day, from days 6-15 of gestation, had no effect upon reproductive performance in dams although weight gain was significantly inhibited at the high concentration. There were no fetal malformations at 0 or 50 ppm. At 150 ppm, pups from 3/29 treated litters had multiple (primarily skeletal) malformations. The incidence of fetuses with hypoplastic tails was higher than historical controls but not statistically significantly higher than concurrent controls.

Although this incidence was not statistically different from control rats, in a second reproductive study, Pietrowicz et al. (1980) stated in an abstract that treatment of rat dams by an unspecified route with 25-400 mg/kg ethyl acrylate during gestation was associated with decreased body and placental weight gains, increased numbers of resorptions and skeletal abnormalities.

In the 2-year gavage study by NTP (1986a), rats and mice had dose-related increases in forestomach hyperplasia, hyperkeratosis, inflammation or ulceration at $\geq$100 mg/kg, 5 days/week. The only effect in rats treated with ethyl acrylate in the drinking water at concentrations up to 2000 ppm or dogs treated orally by capsule with up to ≈931 ppm (TWA) was decreased body weight gain in high-dose female rats (Borzelleca et al., 1964).

In F344 rats given 0-110 mg/kg ethyl acrylate by gavage 5 times/week for 13 weeks, there were no treatment-related effects on body weight gain, longevity or clinical signs (NTP, 1986a). The only prominent histopathological change, occurring in the high-dose males, was an occasional reddened duodenum or pronounced stomach vasculature. Administration of up to 100 mg/kg ethyl acrylate to male and female B6C3F1 mice on the same treatment schedule had no effects on longevity, body weight gain or gross or microscopic histopathology (NTP, 1986a). Similar results were obtained by Treon et al. (1949) in two rabbits given 31.5 mg/kg ethyl acrylate orally, 5 times/week for 7 weeks. In a series of 14-day oral studies, the NTP (1986a) determined that gavage administration of 100 mg/kg/day ethyl acrylate in rats and 200 mg/kg/day ethyl acrylate in mice led to abdominal adhesions, thickened forestomach mucosa and nonulcerative inflammation. Administration of higher doses resulted in ulcers and more severe inflammation. Oral LD_{50} values ranging from 0.35-1.8 g/kg have been reported (Tanii and Hashimoto, 1982; Pozzani et al., 1949; Treon et al., 1949).

In the chronic inhalation study, nonneoplastic lesions of the nasal mucosa (e.g., hyperplasia, mineralization, inflammation, metaplasia) occurred in mice and rats at exposures ≥25 ppm (≥102 mg/m³), 6 hours/day, 5 days/week for up to 27 months (Miller et al., 1985). Exposure to 5 ppm, 6 hours/day, 5 days/week had no effect.

Inhalation exposure to lethal concentrations (1090 mg/m³, 7 hours/day for 28 days) of ethyl acrylate led to weight loss and severe signs of mucosal irritation in rats, guinea pigs, rabbits and in one monkey (Treon et al., 1949); these signs included conjunctivitis, lethargy and diarrhea. Examination of poisoned rats, guinea pigs and rabbits revealed multiorgan involvement and a variety of edematous and degenerative changes. These changes were found to be reversible in survivors that were sacrificed 2 months after termination of exposure. Exposure at 70 ppm (287 mg/m³) for 7 hours/day in rabbits, guinea pigs, rats and monkeys was without adverse effects (Pozzani et al., 1949; Treon et al., 1949). Lomonova and Klimova (1979) determined LC_{50s} of 16,200 and 7500 mg/m³ for unspecified durations for mice and rats, respectively.

Ethyl acrylate is a potent skin irritant (Pozzani et al., 1949; Treon et al., 1949) inducing erythema, edema, cellular necrosis and abscesses. Corneal necrosis after ocular application in rabbits was observed by Pozzani et al. (1949).

A q_1^* of 4.8×10^{-2} $(mg/kg/day)^{-1}$ was derived based on the incidence of squamous cell papillomas/carcinomas of the forestomach in male rats in the NTP (1986a) study. The concentration of ethyl acrylate in drinking water associated with increased lifetime risk of cancer at levels of 10^{-5}, 10^{-6} and 10^{-7} are 7.3×10^{-3}, 7.3×10^{-4} and 7.3×10^{-5} mg/ℓ, assuming that a 70 kg man consumes 2 ℓ water/day. An F factor of 2.16×10^{-1} $(mg/kg/day)^{-1}$ was also derived from the tumor response data in male rats.

Since the F factor is <1, ethyl acrylate is placed in Potency Group 3. Since there was sufficient evidence that ethyl acrylate is carcinogenic in animals, but suggestive evidence that it is carcinogenic in humans, ethyl acrylate is classified as a U.S. EPA Group B2 chemical at this time, that is, a probable human carcinogen. However, this chemical is currently under Agency review. This additional evidence, expected in a few weeks, may necessitate a re-evaluation upward to a B1 chemical. A Potency Group 3 and U.S. EPA Group B2 chemical has a LOW hazard ranking under CERCLA.

An RQ of 1000 was derived based on the observation of respiratory metaplasia in mice in the chronic inhalation study by Miller et al. (1985).

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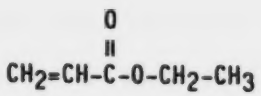
LIST OF ABBREVIATIONS

BOD	Biological oxygen demand
BODT	Biological oxygen demand theoretical
BUN	Blood urea nitrogen
CHL	Chinese hamsters lung
CNS	Central nervous system
CS	Composite score
GRAS	Generally recognized as safe
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PCV	Packed cell volume
PEL	Permissible exposure level
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SGPT	Serum glutamic pyruvic transaminase
SMR	Standardized mortality ratio
STEL	Short-term exposed level
TLV	Threshold limit value
TOTP	Tri-o-tolyl phosphate
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Ethyl acrylate is the common name for the compound 2-propenoic acid, ethyl ester (Chemical Abstract Service designation). Synonyms for ethyl acrylate include ethyl 2-propenoate, ethoxycarbonylethylene and acrylic acid, ethyl ester. The structure, molecular weight, empirical formula and CAS number for ethyl acrylate are as follows:



Molecular weight: 100.12

Empirical formula: $C_5H_8O_2$

CAS number: 140-88-5

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Ethyl acrylate is a colorless liquid with an acrid odor (Windholz, 1983). It is soluble in alcohol, ether and chloroform (Weast, 1985). Selected physical properties are as follows:

Melting point:	-71.2°C	Weast, 1985
Boiling point:	99.8°C	Weast, 1985
Density:	0.9234 g/cm³ (20/4°C)	Weast, 1985
Refractive index:	1.4068 (20°C)	Weast, 1985
Water solubility		
at 20°C:	2.0 g/100 mℓ water	Windholz, 1983
at 25°C:	1.8 g/100 g water	Klein, 1981
Vapor pressure		
at 20°C:	31 mm Hg	Union Carbide, 1979
at 26°C:	40 mm Hg	Perry and Green, 1984
Log K_{ow}:	1.33	Hansch and Leo, 1985

Vapor density: (air = 1)	3.45	Windholz, 1983
Flash point:	15°C (open cup)	Windholz, 1983
Conversion factors: (air)	1 mg/m³ = 0.24 ppm 1 ppm = 4.16 mg/m³	Verschueren, 1983

Ethyl acrylate easily polymerizes on standing (Windholz, 1983); the commercial material may contain from 15-200 ppm hydroquinone monomethyl ether or 1000 ppm hydroquinone as an inhibitor (IARC, 1977). Polymerization is accelerated by heat, light and peroxides (Windholz, 1983). Ethyl acrylate is flammable and can be a dangerous fire and explosion hazard (Hawley, 1981).

1.3. PRODUCTION DATA

Commercial production of ethyl acrylate was first reported in the United States in 1944 (IARC, 1979b). In 1984, three U.S. manufacturers (Celanese, Rohm and Haas, and Union Carbide) reported production of 306.4 million pounds (USITC, 1985). The current U.S. manufacturers of ethyl acrylate include Badisch Corp. (Freeport, TX), Celanese Corp. (Clear Lake, TX; Pampa, TX), Rohm and Haas Co. (Deer Park, TX) and Union Carbide (Taft, LA) (SRI, 1986).

Ethyl acrylate is manufactured in the United States by a propylene oxidation process (SRI, 1986). In this process, acrolein is first formed by the catalytic oxidation of propylene vapor at high temperatures in the presence of steam and then oxidized with O_2 to yield acrylic acid (Kine and Novak, 1978). The acrylic acid is then esterified with ethyl alcohol.

1.4. USE DATA

Ethyl acrylate is the most widely used acrylate ester (Celanese Chemical Co., 1981) and is used as a monomer in the production of a variety of polymer products (IARC, 1979b). It is used to produce flexible resins for

water-based paints and adhesives, textile, paper and leather-finishing resins, and has wide usage in industrial metal finishing with solution polymers (Celanese Chemical Co., 1981). Ethyl acrylate is a major component of acrylic emulsion polymers used in latex paints for exterior house and trim, and interior wall semi-gloss and trim. It is also used for the production of acrylic fibers (IARC, 1979b).

1.5. SUMMARY

Ethyl acrylate is a colorless liquid with an acrid odor (Windholz, 1983). It is soluble in alcohol, ether and chloroform, and is reasonably soluble (~2% by weight) in water (Weast, 1985; Windholz, 1983). It is a monomer used in the production of a variety of polymers, such as flexible resins for latex paints, textile, paper and leather-finishing resins, and solution polymers for metal finishing and for the production of acrylic fibers (Celanese Chemical Co., 1981; IARC, 1979b). In 1984, three U.S. manufacturers reported production of 306.4 million pounds of ethyl acrylate (USITC, 1985). Currently, four manufacturers at five locations produce this chemical in the United States (SRI, 1986).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

If released to water or soil as in the case of a spill, ethyl acrylate is likely to undergo polymerization to an innocuous resin (U.S. EPA-NIH, 1986). The polymerized acrylate is insoluble and will sink in water. The fate processes discussed below relate to dilute concentrations of ethyl acrylate, which may be encountered in the environment; these dilute concentrations are unlikely to experience significant polymerization.

2.1. WATER

2.1.1. Hydrolysis. The hydrolysis half-life for ethyl acrylate at 25°C and pH 7 has been reported to be 3.5 years (Mabey and Mill, 1978). Based on the acid- and base-catalyzed hydrolysis rate constants reported by Mabey and Mill (1978), hydrolysis in environmentally acidic waters will be even slower. Hydrolysis in alkaline waters will be accelerated, however; at pH 8 and 25°C, the half-life will be on the order of 100 days, while at pH 9, the half-life will be ~10 days. Therefore, hydrolysis will not be important in environmental waters at pH <9. The hydrolysis products, should hydrolysis occur, will be acrylic acid and ethanol.

2.1.2. Oxidation. Experimental data specific to the oxidation of ethyl acrylate in water could not be located in the available literature as cited in the Appendix; however, oxidation of unsaturated compounds by photochemically produced oxidants such as singlet oxygen and HO radical is potentially an important removal mechanism (Mill and Mabey, 1985). The half-life for the reaction of singlet oxygen with ethyl acrylate in the gas phase has been reported to be $>1.54 \times 10^4$ M^{-1} sec^{-1} (Datta and Rao, 1979). Assuming that the reactivity of acrylate monomers in water is similar to that in the

gas phase and that the concentration of singlet oxygen in natural water is 10^{-12} M (Mill and Mabey, 1985), the half-life for this reaction is estimated to be >1 year.

The half-life of olefins in water from reaction with HO radical is on the order of 13-14 days (Mill and Mabey, 1985). The olefin-structured acrylate monomers may again be susceptible to this oxidation process. Oxidation of olefins with RO_2 radical in water has a reported half-life >200 years; therefore, this oxidation reaction is not important.

2.1.3. Photolysis. In cyclohexane, acetonitrile and methanol solvents, the ethyl and methyl esters of acrylic and methacrylic acids do not absorb light strongly in the UV spectrum ~290 nm (Brunn et al., 1976). Based on the absorption spectrum of acrolein (U.S.EPA, 1979), ethyl acrylate may have moderate UV absorption at wavelengths >300 nm. This suggests that direct photolysis in water may occur, although the significance of this process cannot be predicted unless more photolytic data are available.

2.1.4. Microbial Degradation. Price et al. (1974) measured the biodegradability of ethyl acrylate in BOD tests using an acclimated and nonacclimated sewage seed in freshwater and a nonacclimated sewage seed in synthetic seawater. In the freshwater, 5-day and 20-day BODTs of 28 and 35%, respectively, were observed with the nonacclimated seed, while respective BODTs of 66 and 79% were observed with the acclimated seed. In the synthetic seawater, 5-day and 20-day BODTs of 11 and 53% were observed, respectively.

Ethyl acrylate was confirmed to be significantly biodegradable (biooxidation was >30% after 2 weeks of incubation) by the Japanese MITI test (Sasaki, 1978). Thom and Agg (1975) have reported that ethyl acrylate should be degradable by biological sewage treatment provided suitable acclimatization can be achieved.

Chou et al. (1979) used an anaerobic reactor with an upflow filter to determine that ethyl acrylate at a concentration of 500 mg/ℓ was toxic at least to some microorganisms. At a concentration of 100 mg/ℓ, however, ethyl acrylate was 95% utilized. Speece (1983) suggested that ethyl acrylate should be amenable to anaerobic biodegradation under industrial wastewater treatment conditions.

2.1.5. Volatilization. Based on a vapor pressure of 31 mm Hg (Union Carbide, 1979) and a water solubility of 20 g/ℓ (Windholz, 1983) at 20°C, the Henry's Law constant for ethyl acrylate can be estimated to be 2×10^{-4} atm-m³/mol. This value of Henry's Law constant indicates that volatilization will be significant from all environmental waters (Lyman et al., 1982). Using the method of Lyman et al. (1982), the volatilization half-life from a river 1 meter deep flowing 1 m/sec with a wind velocity of 3 m/sec is estimated to be 7.2 hours. The volatilization half-life from a river 10 m deep is estimated to be 7.6 days.

2.1.6. Adsorption. Based on a water solubility of 20 g/ℓ at 20°C (Windholz, 1983) and a log K_{ow} of 1.33 (Hansch and Leo, 1985), partitioning from the water column to particulate organic matter and sediment is not expected to be important.

2.1.7. Bioconcentration. The following two equations have been used for estimating the BCF (Lyman et al., 1982):

$$\log BCF = 0.76 \log K_{ow} - 0.23 \qquad (2\text{-}1)$$

$$\log BCF = 2.791 - 0.564 \log WS \text{ (in ppm)} \qquad (2\text{-}2)$$

Based on a log K_{ow} of 1.33 and a water solubility of 20 g/ℓ at 20°C, the BCF values estimated from Equations 2-1 and 2-2 for ethyl acrylate are 6 and 2, respectively. These values suggest that bioaccumulation of ethyl acrylate in aquatic organisms will not be significant.

2.2. AIR

Because of its relatively high vapor pressure, ethyl acrylate that is released to the atmosphere is expected to remain in the vapor-phase and not become associated with particulate matter.

The rate constants for the vapor-phase atmospheric reaction of ethyl acrylate with HO radical and with ozone have been estimated to be 2.7×10^{-11} cm³ molecule-sec (HO radical) and 1.3×10^{-16} cm³/molecule-sec (O_3) (U.S. EPA, 1986). Assuming average atmospheric concentrations of 8×10^5 HO radical molecules/cm³ and 6×10^{11} O_3 molecules/cm³, the half-life of ethyl acrylate (with respect to the combined effect of HO radical and O_3) has been estimated to be 6.5 hours (U.S. EPA, 1986). The half-lives with respect to only HO radical or O_3 can be calculated to be 8.9 and 24.7 hours, respectively.

The significance of direct photolysis in determining the fate of atmospheric ethyl acrylate cannot be assessed because of the lack of relevant data.

2.3. SOIL

2.3.1. Microbial Degradation. Pertinent data regarding the microbial degradation of ethyl acrylate in soil could not be located in the available literature as cited in the Appendix. Since ethyl acrylate has been shown to be degradable in various BOD tests (see Section 2.1.4.), microbial degradation in soil is possible.

2.3.2. Adsorption. K_{oc} values can be estimated using the following two regression equations (Lyman et al., 1982):

$$\log K_{oc} = 3.64 - 0.55 \log WS \text{ (in ppm)} \qquad (2\text{-}3)$$

$$\log K_{oc} = 0.544 \log K_{ow} + 1.377 \qquad (2\text{-}4)$$

The K_{oc} values calculated from Equations 2-3 and 2-4 for ethyl acrylate (log K_{ow} of 1.33; water solubility of 20,000 ppm) are 19 and 126, respectively. These estimated K_{oc} values predict high to very high soil mobility (Swann et al., 1983). Therefore, ethyl acrylate appears susceptible to significant leaching in soil.

2.3.3. Volatilization. The vapor pressure of ethyl acrylate (31 mm Hg at 20°C) indicates that it will volatilize from dry surfaces quite rapidly. In moist soils, volatilization may be significant since ethyl acrylate is expected to significantly volatilize from water (see Section 2.1.5.).

2.3.4. Hydrolysis. The aqueous hydrolysis of ethyl acrylate is not expected to become environmentally important until the pH is $\geq$9 (see Section 2.1.1.). In moist alkaline soils (pH$\geq$9), hydrolysis is potentially important.

2.4. SUMMARY

Ethyl acrylate is likely to undergo polymerization to an innocuous resin if released to the environment in a spill-type situation (U.S. EPA-NIH, 1986); however, the diluted concentrations, which may be encountered in the environment, are unlikely to polymerize significantly. If released to water, volatilization and indirect photooxidation (by hydroxyl radicals) are expected to be important removal mechanisms. The role of direct photolysis cannot be assessed with the data currently available. Ethyl acrylate has been shown to be significantly biodegradable in two BOD studies (Sasaki, 1978; Price et al., 1974), which suggests that biodegradation in the environment is possible. Adsorption onto sediment, bioconcentration and hydrolysis (except if pH$\geq$9) are not expected to be important in the aquatic environment. If released to the atmosphere, ethyl acrylate is expected to remain in the vapor-phase and react rapidly with HO radical and ozone, with

an estimated half-life of 6.5 hours (U.S. EPA, 1986). If released to soil, ethyl acrylate is expected to be highly mobile based on estimated K_{oc} values; therefore, significant leaching in soil may occur. Ethyl acrylate may volatilize significantly from soil surfaces. In moist alkaline soils ($pH \geq 9$), hydrolysis is potentially important.

3. EXPOSURE

3.1. WATER

Pertinent monitoring data regarding methyl acrylate in water could not be located in the available literature as cited in the Appendix. The U.S. EPA STORET database contained no postings for the compound.

It is possible that ethyl acrylate may be discharged with wastewater effluents generated during its manufacture and use operations. Small amounts of residual ethyl acrylate monomer have been found in polyethyl acrylate (Brunn et al., 1975) and in polymer latexes used in the paper and textile industries (Bollini et al., 1975). Leaching of residual monomer from polymer products, which have been landfilled, may be possible, although no monitoring data is available to confirm this suggestion.

3.2. FOOD

Ethyl acrylate has been reported to be a volatile component of pineapple concentrate (Näf-Müller and Willhalm, 1971).

The U.S. Food and Drug Administration (1977) considers ethyl acrylate to be a GRAS adjuvant in food and polymers, and copolymers made from ethyl acrylate are permitted for various contact uses with foods. Residual monomer in these polymers and copolymers may leach into the contacted foods; however, no data are available to confirm this.

3.3. INHALATION

Pertinent monitoring data regarding ethyl acrylate in ambient air could not be located in the available literature as cited in the Appendix; however, ambient atmospheric emissions may result from its manufacture and use. Ethyl acrylate was identified in an effluent gas stream from a company involved in painting and printing in Japan (Yasuhara et al., 1984).

Kiselev et al. (1983) detected ethyl acrylate in the volatile emissions from a plastic material (Acronal 800) used in the building construction industry in the USSR.

Samimi and Falbo (1982) detected mean TWA ethyl acrylate concentrations of <1-55 ppb in the breathing zone of workers working near polymerization reactors in a polystyrene production plant. Workers at unloading docks had a mean TWA concentration of 211 ppb. Szczebara et al. (1983) found ethyl acrylate concentrations of 0.7-21 mg/m³ in the air at the unwoven fabrics division of a textile plant in Poland.

The high temperature degradation of polydimethacrylates can result in the formation of ethyl methacrylate (Lomakin et al., 1984), suggesting that incineration of methacrylate polymers may produce ethyl methacrylate as a combustion product, which may in turn be released to the atmosphere through stack emissions. Incineration of acrylate polymers may therefore be a source of atmospheric release of ethyl acrylate.

3.4. DERMAL

Pertinent data regarding dermal exposure to methyl acrylate could not be located in the available literature as cited in the Appendix. Exposure potential may be greatest in occupational settings.

3.5. SUMMARY

Pertinent ambient air or water monitoring data regarding ethyl acrylate could not be located in the available literature as cited in the Appendix. It is possible that ethyl acrylate will be emitted to the atmosphere or to water from effluents produced during its industrial manufacture or use. Leaching of residual monomer from polymer products, which have been land-filled, may be possible. Ethyl acrylate has been reported to be a volatile component of pineapple concentrate (Näf-Müller and Willhalm, 1971). Polymer

products made from ethyl acrylate are permitted for various food contact uses (U.S. FDA, 1977), suggesting that leaching of residual monomer into foods may be possible. Incineration of acrylate polymers may be a source of atmospheric release.

4. PHARMACOKINETICS

4.1. ABSORPTION

NTP (1986a) gave three male and three female Fischer 344 rats 200 mg/kg ethyl acrylate as a 4% solution in corn oil by gavage. At 15, 30 and 60 minutes postadministration, 50 µℓ samples of intraocular blood were taken. Venepuncture of the exposed portal vein was done 15 and 30 minutes post-administration and 50 µℓ samples were withdrawn. Determination of ethyl acrylate content was made on both sets of samples by gas chromatography. The NTP (1983) found no ethyl acrylate in the intraocular samples at any time (detection limit = 1 µg/mℓ), but did detect 4-27 µg/mℓ in the portal blood at 15 minutes and ~1-18 µg/mℓ at 30 minutes after dosing. Although the results do not provide sufficient data regarding the extent or rate of absorption, they suggest that gastrointestinal absorption of ethyl acrylate does occur after oral administration.

Stott and McKenna (1984) studied ethyl acrylate vapor absorption in isolated preparations of upper and lower rat respiratory tracts and in the intact rat. The investigators estimated that 30-70% of the inhaled ethyl acrylate was absorbed by the upper respiratory tract. Similar percentages were absorbed by the lower respiratory tract and the intact rat.

4.2. DISTRIBUTION

Data regarding the distribution of ethyl acrylate are limited. Treon et al. (1949) reported that the odor of ethyl acrylate was noticeable in all tissues and especially in the stomachs of rabbits given single oral doses $\geq$420 mg/kg.

4.3. METABOLISM

In the NTP (1983) experiments, groups of six F344 rats were given either 100 or 200 mg/kg ethyl acrylate in corn oil by gavage. The rats were killed

at 30 or 120 minutes after dosing and the stomachs removed. Nonprotein thiol concentrations were found to be reduced, relative to control values, both in the glandular stomach and, especially, in the forestomach. Reduction of forestomach concentrations was slightly greater after the 120-minute kill, and at the higher dose. The percentages of parent compound remaining in the stomach were 29-40% after 30 minutes.

The forestomachs and glandular stomachs, including contents, were removed from six untreated F344 rats (three males and three females) for determination of *in vitro* metabolism (NTP, 1986a). After removal of the stomach contents, all three components were homogenized, and 5 mℓ aliquots of each homogenate were incubated with 150 µg ethyl acrylate. Between 5 and 65 minutes after the onset of incubation, 200 µℓ aliquots were transferred to vials, where an internal standard was added. After mixing, a 1 µℓ aliquot was withdrawn and gas chromatographed. Blood samples for determination of ethyl acrylate half-lives were taken from anesthetized rats, and the incubation processes were conducted (with 500 µg ethyl acrylate) similarly to those of the stomach tissues. Aliquots were removed for chromatographic analysis at 1.5-2.5 minutes after the onset of incubation.

Metabolism of ethyl acrylate was first order in homogenates of the forestomach, glandular stomach and stomach contents. Half-lives for the disappearance of the parent compound from the forestomach, glandular stomach and stomach contents in male rats were 76, 67 and 53 minutes, respectively, and in female rats were 96, 66 and 73 minutes, respectively. *In vitro* metabolism in blood was much faster; the average half-lives in three males was 14.0 minutes and the average in females was 11.8 minutes. These experiments indicate that metabolism of ethyl acrylate can take place in the stomach and in the blood.

Silver and Murphy (1981) showed that rat lung, kidney and liver homogenates were capable of hydrolyzing ethyl acrylate to acrylic acid by tissue carboxylesterase. Pretreatment with 5-125 mg/kg TOTP, a carboxylesterase inhibitor, in independent groups of rats reduced hydrolysis 36-97% in these tissues. After pretreatment with 125 mg/kg TOTP, rats exposed by inhalation for 4 hours to 300-1000 ppm (1228-4095 mg/m^3) ethyl acrylate had significantly decreased lung, blood, kidney and liver nonprotein sulfhydryl levels, relative to rats given a corn oil pretreatment. These results suggest the importance of the carboxylesterase-mediated ethyl acrylate metabolism and the shift to a conjugation reaction when that mechanism is inhibited.

Miller et al. (1981) observed hydrolysis of ethyl acrylate to acrylic acid in rat liver, lung and kidney homogenates. When added to blood in vitro, however, acrylic acid formation was not apparent. Rather, the parent ester was found to bind to nonprotein sulfhydryl groups.

4.4. EXCRETION

Pertinent data regarding the excretion of ethyl acrylate could not be located in the available literature as cited in the Appendix.

4.5. SUMMARY

Pertinent data regarding the extent and rate of absorption of ethyl acrylate are limited. In rats given a single oral dose of 200 mg/kg ethyl acrylate, there was no parent compound detected in intraocular blood 15-60 minutes postadministration, but there were detectable portal blood levels 15-30 minutes after dosing. These results suggest that ethyl acrylate is absorbed by the gastrointestinal tract.

Stott and McKenna (1984) estimated that 30-70% of an inhaled concentration of ethyl acrylate was absorbed into the bloodstream by the upper respiratory tract of rats. The NTP (1986a) found half-lives of 53-76 minutes

in male rats and 66-96 minutes in females for metabolism of ethyl acrylate in individual homogenates of the forestomach, glandular stomach and stomach contents. In vitro blood half-lives were 11.8 and 14.0 minutes for female and male rats, respectively. Nonprotein thiol concentrations were reduced in the isolated stomachs of rats following oral dosing with ethyl acrylate. Rat lung, kidney and liver homogenates hydrolyzed ethyl acrylate to acrylic acid by tissue carboxylesterase (Miller et al., 1981; Silver and Murphy, 1981). In rat blood, however, no acrylic acid was formed, but ethyl acrylate was bound to nonprotein sulfhydryl groups (Miller et al., 1981). Inhibition of carboxylesterase activity in rats increased the conjugation reactions in the lungs, blood, liver and kidneys (Silver and Murphy, 1981). Thus, ethyl acrylate can be hydrolyzed to acrylic acid or conjugated to nonprotein sulfhydryl groups, presumably glutathione, in competitive pathways. Pertinent data regarding the excretion of ethyl acrylate could not be located in the available literature as cited in the Appendix.

5. EFFECTS

5.1. CARCINOGENICITY

5.1.1. Experimental Studies. The NTP (1986b) has listed a 2-year carcinogenicity bioassay of oral ethyl acrylate in F344/N rats and B6C3F1 mice, which is in final printing. In this study groups of 50 male and 50 female F344/N rats and B6C3F1 mice received ≥99% pure ethyl acrylate in corn oil by gavage, 5 days/week for 103 weeks. Dose levels were 0, 100 and 200 mg/kg. All animals were weighed weekly for the first 12 weeks and monthly thereafter and were observed twice daily for mortality and morbidity. Gross and comprehensive histological examinations were performed on all animals that died, were killed when moribund or were killed 1-2 weeks after the treatment was discontinued.

There were no significant differences in survival for treated rats and mice compared with controls. Survival was 64-84% for rats and 52-72% for mice. The most prominent neoplastic lesions were found in the forestomach (Table 5-1). By the Life Table, Incidental Tumor and Fisher Exact tests, administration of the high dose significantly ($p<0.001$) increased the incidences of squamous cell papilloma, carcinoma and combined papilloma/carcinoma in the forestomachs of male rats over control values. Incidences of squamous cell papilloma and papilloma/carcinoma were significantly increased ($p<0.001$) at 100 mg/kg doses; administration of the low dose increased the incidence of squamous cell carcinoma at $p<0.05$, by all three methods of statistical analysis. For the three forestomach tumor classifications, the Cochran-Armitage, Life Table and Incidental Tumor tests for trends were statistically significant for males ($p<0.001$). Forestomach tumor incidence was less pronounced in treated female rats. Administration of the high dose led to statistically significant increases in the incidences of squamous cell papillomas and combined papillomas/carcinomas

TABLE 5-1

Forestomach Squamous Cell Tumors in Male and Female F344 Rats and B6C3F1 Mice Given 99% Pure Ethyl Acrylate in Corn Oil by Gavage 5 Days/Week for 103 Weeks and Sacrificed After 104-105 Weeks[a]

Species/Strain	Sex	Dose (mg/kg)	Tumor Type	Tumor Incidence (p value)[b,c]
Rat/F344	M	0	papilloma	1/50 (p<0.001)
		100		15/50 (p<0.001)
		200		29/50 (p<0.001)
		0	carcinoma	0/50 (p<0.001)
		100		5/50 (p=0.028)
		200		12/50 (p<0.001)
		0	combined	1/50 (p<0.001)
		100	papilloma/	18/50 (p<0.001)
		200	carcinoma	36/50 (p<0.001)
Rat/F344	F	0	papilloma	1/50 (p=0.008)
		100		6/50 (p=0.056)
		200		9/50 (p=0.008)
		0	carcinoma	0/50 (p=0.095)
		100		0/50
		200		2/50 (p=0.247)
		0	combined	1/50 (p=0.002)
		100	papilloma/	6/50 (p=0.056)
		200	carcinoma	11/50 (p=0.002)
Mouse/B6C3F1	M	0	papilloma	0/48 (p=0.002)
		100		4/47 (p=0.056)
		200		9/50 (p=0.002)
	M	0	carcinoma	0/48 (p=0.019)
		100		2/47 (p=0.242)
		200		5/50 (p=0.031)
	M	0	combined	0/48 (p<0.001)
		100	papilloma/	5/47 (p=0.026)
		200	carcinoma	12/50 (p<0.001)

TABLE 5-1 (cont.)

Species/Strain	Sex	Dose (mg/kg)	Tumor Type	Tumor Incidence (p value)[b,c]
Mouse/B6C3F1	F	0	papilloma	1/50 (p=0.072)
		100		4/49 (p=0.175)
		200		5/48 (p=0.093)
	F	0	carcinoma	0/50 (p=0.135)
		100		1/49 (p=0.495)
		200		2/48 (p=0.237)
	F	0	combined papilloma/ carcimona	1/50 (p=0.022)
		100		5/49 (p=0.098)
		200		7/48 (p=0.026)

QUALITY OF EVIDENCE

Strengths of Study: Adequate number of animals for a lifetime bioassay. Multiple histopathological endpoints explored. Appropriate dose levels used. Oral route of exposure.

Weaknesses of Study: Neoplastic response may be secondary to mucosal irritation induced by gavage administration.

Comments: Adequate

[a]Source: NTP, 1986a

[b]Probability level for control groups represents dose-related trend by the Cochran-Armitage test

[c]Probability level for treated groups represents treated vs. control comparison by Fisher Exact test.

($p<0.05$ by the Life Table, Incidental Tumor and Fisher Exact tests), but not in the incidence of squamous cell carcinomas. The occurrences of papilloma and papillomas/carcinomas in the 100 mg/kg dose group were significant by the incidental tumor test ($p=0.034$ in both cases), but not by the Fisher Exact or Life Table tests. Finally, the Cochran-Armitage, Life Table and Incidental Tumor trend tests were statistically significant ($p<0.01$) for papillomas and papillomas/carcinomas.

Low-dose male rats were found to have increased incidences of pancreatic acinar cell tumors ($p=0.041$) and mononuclear cell leukemia ($p=0.035$) by the Life Table test. No acinar cell tumors and only 1/49 mononuclear cell leukemia were observed in high-dose males; therefore, because of the absence of a dose-response, the investigators did not place any biological significance upon these findings. They also did not consider findings of negative dose-related trends in the incidences of basal cell tumors of the skin and testicular interstitial cell tumors to be toxicologically significant. A negative dose-related trend for the incidence of benign adrenal pheochromocytomas in male rats (controls 15/50; low dose, 13/49; high dose 5/50), statistically significant by the Cochran-Armitage test ($p=0.011$) was considered by the authors to be treatment-related but the mechanism for reduced tumor incidences is unknown.

As with the rats, the incidences of squamous cell papillomas and carcinomas of the forestomach in mice were dose-related (see Table 5-1). Life Table, Cochran-Armitage and Incidental Tumor tests for trend were significant ($p<0.03$) for papillomas, carcinomas and combined papillomas/carcinomas. At 100 mg/kg, the Fisher Exact test showed that the 100 mg/kg group had significantly greater ($p=0.026$) forestomach papillomas/carcinomas than

controls; no other comparison at this dose level was statistically significant. For the high-dose males, there were increased ($p<0.05$) incidences of squamous cell papillomas, carcinomas and combined papillomas/carcinomas by all three statistical tests (Fisher, Life Table and Incidental Tumor tests). In females, there were nonstatistically significant ($p>0.05$) trends toward dose-related increases in squamous cell papillomas and carcinomas, when each tumor type was analyzed separately. When analyzed as combined papilloma/carcinoma occurrences, the Cochran-Armitage, Life Table and Incidental Tumor tests for trend were significant ($p\sim0.02$). The combined tumor incidence was increased in the low-dose group, but not significantly; in high-dose females, the incidence was statistically significantly increased ($p<0.05$ by the Fisher, Life Table and Incidental Tumor tests). The separate tumor incidences were not significantly increased above controls in either treated group by any test.

Significant negative trends for hepatocellular tumors, follicular cell tumors of the thyroid, lymphocytic lymphoma in male mice and significantly lower incidences of pituitary adenomas in female mice compared with controls were considered to be treatment-related, but the mechanism is unknown.

NTP (1986a) concluded that ethyl acrylate was carcinogenic in rats and mice.

In a 2-year study, Borzelleca et al. (1964) exposed groups of 25 male and 25 female Wistar rats to ethyl acrylate in the drinking water at concentrations of 0, 6, 60 or 2000 ppm. During the 5th month, the 6 and 60 ppm levels were raised to 7 and 70 ppm. There was no efffect on survival. No evidence of carcinogenicity was found upon sacrifice of the 2-year survivors and histological examination of heart, lung, liver, kidney, urinary bladder, spleen, gastroenteric, skeletal muscle, bone marrow, skin, brain, thyroid, adrenal, pancreas, pituitary and gonads.

Miller et al. (1985) exposed male and female B6C3F1 mice and F344 rats to 0, 25, 75 or 225 ppm (0, 102, 307 or 921 mg/m³) >99.5% pure ethyl acrylate vapors for 6 hours/day, 5 days/week (excluding "holidays"). For the 225 ppm group, exposure was discontinued after 6 months and survivors were maintained for an additional 21 months. Interim sacrifices were performed at 3, 6, 12 and 18 months for rats and 6, 12 and 18 months for mice. The remaining 60 rats and 60 mice of each sex were maintained as controls and 75 rats and 75 mice of each sex were used in the treated groups. Except for the high-dose group, all rats and mice were treated for 27 months. Surviving rats and mice were examined monthly for palpable masses. Rats and mice that died during the 27-month exposure period, or killed when moribund, were examined grossly. At the end of 27 months, survivors were sacrificed and gross pathologies performed on ~50 tissues. Histological examinations of all these tissues (except female mammary tissue and rectum) were performed for rats and mice in the control and 75 ppm groups. Histological examinations of a more limited set (~15) of tissues were performed on rats and mice exposed to 25 and 225 ppm. In all groups, nasal cavities were processed and examined at four cross-sectional levels. Only observations on tissues that were examined histologically were analyzed statistically.

Ethyl acrylate exposure did not affect the longevity of either sex of mice or rats. In addition, there were no significant differences in incidences of palpable masses throughout the study. The major pathological effects found in both rats and mice were nonneoplastic changes in the olfactory epithelium (Section 5.5.). In the male rats, Fisher's Exact tests revealed no significant increases in total benign or total malignant tumor incidence that were due to treatment, although (as shown in Table 5-2) there was a statistically significant ($p<0.05$) increase in follicular thyroid adenoma/adenocarcinomas, compared with combined control data, at 25 ppm.

TABLE 5-2

Incidence of Follicular Thyroid Adenomas/Adenocarcinomas in Male and Female F344 Rats and B6C3F1 Mice Exposed by Inhalation to >99.5% Pure Ethyl Acrylate Vapors 6 Hours/Day, 5 Days/Week for up to 27 Months[a]

Species/Strain	Sex	Dose (ppm)	Tumor Incidence (p value)[b]
Rat/F344	M	0 (A)[c]	1/60
		0 (B)[c]	0/60
		25	5/76 (p<0.05)
		75	2/75 (NS)
		225[d]	3/71 (NS)
	F	0 (A)	0/59
		0 (B)	0/62
		25	1/77 (NS)
		75	1/78 (NS)
		225	0/70 (NS)
Mouse/B6C3F1	M[e]	0 (A)	1/60
		0 (B)	1/61
		25	1/75 (NS)
		75	0/76 (NS)
		225	7/69 (p<0.05)
	F[f]	0 (A)	13/64
		0 (B)	12/61
		25	7/78 (NS)
		75	7/76 (NS)
		225	5/66 (p<0.05)(N)[g]

QUALITY OF EVIDENCE

Strengths of Study: Chronic inhalation exposure in a sufficient number of rats and mice/group. Adequate concentration range, good control data. Multiple histological endpoints examined.

Weakness of Study: Short daily exposure sessions.

Overall Adequacy: Adequate

[a]Source: Miller et al., 1985
[b]Fisher Exact Test statistic for comparison with combined control groups.
[c]Two independent control groups used for each sex and species
[d]Exposed for 6 months to 225 ppm then held for 21 more months.
[e]Male mouse data for "thyroid adenoma" only
[f]Female mouse data for "thyroid adenomas/adenocarcinomas" only
[g]Significantly lower incidence in treated group compared with controls.
NS = Not significant

This effect was not found at either higher exposure concentrations or in female rats. Cochran-Armitage tests indicated significant dose-related trends in male rats, only for total benign and total malignant tumors. Because there was no consistent pattern of primary tumorigenesis in the males, the investigators considered these results to be a statistical anomaly resulting from random variation.

Miller et al. (1985) noted a statistically significant ($p<0.05$) increase in thyroid adenomas in the male mice exposed to 225 ppm and a decrease ($p<0.05$) in thyroid adenomas/adenocarcinomas in female mice exposed to this concentration. The authors noted that the spontaneous incidence of thyroid tumors was highly variable in B6C3F1 mice. In male B6C3F1 mice, the historical control incidence of thyroid follicular cell adenomas or carcinomas, after gastric incubation in corn oil, ranged from 0/50 to 5/47 (NTP, 1986a). Data on rats or on female mice were not provided in the NTP (1986a) bioassay. Miller et al. (1985) found no other treatment-related increases in the incidences of neoplasia.

Forty male C34/Hej mice were skin painted 3 times/week with 25 µl 99% pure ethyl acrylate (~23 mg/mouse) in acetone (DePass et al., 1984). The mice were 74-79 days old at the start of the study and were treated for their entire lifespan. Each mouse was examined daily for tumor development and complete necropsies were performed on mice that died or were sacrificed when moribund. After sectioning and straining, the dorsal skin and all gross lesions were examined histologically. Forty male mice given either 20 mg/mouse acetone (negative control) or 0.02 mg/mouse 3-methylcholanthrene (positive control) on the same treatment schedule were also used. DePass et al. (1984) found no ethyl acrylate or acetone-induced epidermal tumors. Ethyl acrylate administration also did not affect longevity. Of the mice treated with 3-methylcholanthrene, 39 developed epidermal tumors.

5.1.2 Epidemiological Studies

A series of retrospective epidemiology studies were conducted by Rohm and Haas (1981, 1984, 1986a,b) to determine the effect of exposure to ethyl acrylate and methyl methacrylate on male workers employed at plastics manufacturing plants in Deer Park, TX, Bristol, PA and Knoxville, TN.

Mortality among white males employed at the Texas plant was compared with that for the U.S. white male population (Rohm and Haas, 1981). All white males, based on the year of their hire, were assigned to one of six 5-year cohorts than spanned the years 1948-1977. The total of 1849 white males was followed until December 31, 1978. Vital status was compiled for 96% of the white male employees both hourly and salaried. At the end of the follow-up period 89.9% of the cohort were alive, 3.8% status unknown and 6.3% had died. Of the 1372 hourly employees, 90.6% were alive, 3.3% status unknown and 6.1% were dead.

As summarized in Table 5-3, total deaths from all causes showed no significant excesses of observed over expected. Observed cancer deaths (20) were 86.6% of the expected (23.1) (SMR=87). Observed number of respiratory cancers tend to be numerically higher than expected for hourly men with <5 years work exposure, but this difference was not statistically significant. When all hourly employees were grouped together by year of hire, there is a significant excess of other and unspecified cancers and in lymphatic cancers. All other sites showed no significant increased incidence.

The results of a mortality study among Bristol, PA plant employees (Rohm and Haas, 1984) are summarized in Table 5-4. The study population included all white hourly employed workers hired between January 1, 1933 and December 31, 1945. Of the 3934 hourly employees, 39% (1528) were dead, 12% (481) status unknown and 49% (1920) were alive. Table 5-4 lists the causes of death from all diseases for all employees and for those who held jobs

TABLE 5-3

Observed and Expected Deaths from Selected Causes Among White Male Hourly Employees*
Texas Cohort Study

Cause of Death	All Hourly Employees			Hourly Employees with >10 Years of Observation					
	Any Hourly Work Duration			Any Hourly Work Duration			>5 Years Work Duration		
	O	E	O/E	O	E	O/E	O	E	O/E
All causes	84	121	0.69	54	84.6	0.64	34	59.9	0.57
All malignant neoplasms	20	23.1	0.87	15	17.9	0.84	8	12.7	0.63
Buccal cavity and pharynx	0	0.8	0.00	0	0.64	0.00	0	0.46	0.00
Digestive	3	6.65	0.53	2	4.44	0.45	1	3.10	0.32
Respiratory	7	8.28	0.85	6	6.93	0.87	2	4.94	0.40
Genital	0	0.96	0.00	0	0.72	0.00	0	0.46	0.00
Urinary	1	1.09	0.92	1	0.88	1.14	0	0.62	0.00
Leukemia	1	1.06	0.94	1	0.67	1.49	1	0.47	2.13
Lymphatic	2	1.74	1.15	2	1.12	1.79	2	0.80	2.50
Other cancers	6	3.55	1.69	3	2.52	1.19	2	1.82	1.10

*Source: Rohm and Haas Co., 1981

O = Observed deaths; E = expected deaths; O/E = ratio of observed to expected deaths

Note: A relatively youthful population in which <u>not</u> much site-specificity is exhibited; an additional 10 to 20-year observation period is needed.

TABLE 5-4

Observed and Expected Deaths (1933-1981) from Selected Causes Among Bristol Plant Hourly Employees Hired Before 1946[a]

Deaths	Entire Plant Employees			Employees Ever in Ethyl Acrylate/Methyl Methacrylate Jobs		
	O[b]	E[c]	SMR[d]	O	E	SMR
All causes	1528	1869.2	82	1020	1215.9	84
Disease of the:						
Circulatory system	859	1016.0	85	558	647.8	86
Heart disease	625	685.5	91	407	447.0	91
Cerebrovascular	108	147.5	73	67	89.1	75
All cancers	323	351.8	92	223	234.9	95
Lung cancer	107	104.3	103	67	72.5	93
Colorectal	52	31.2	167[e]	51	29.8	171[e]
Respiratory disease	81	114.3	71	57	73.4	78
Accidents	54	101.6	53	38	70.5	54

[a]Source: Rohm and Haas, 1984

[b]O = Observed deaths

[c]E = Expected deaths

[d]SMR = Ratio of O/E x 100

[e]Statistically significant ($p<0.01$)

involving exposure to ethyl acrylate/methyl methacrylate. The results are similar for both groups of employees. Observed cancer deaths were 92 which is 95% of the predicted value. Lung cancer, the most frequent cause of cancer-related deaths was not significantly increased in either group of employees; however, cancers of the large intestine and rectum were significantly higher than expected [52 observed vs. 31.2 expected, SMR=167 ($p<0.01$); 51 observed vs. 29.8 expected, SMR=171 ($p<0.01$)].

When employee mortality was further analyzed based on years of exposure, age of employee or estimated accumulated dose, the results were inconclusive according to the authors. Risk of colorectal cancers among ethyl acrylate/methyl methacrylate workers did not increase with accumulated dose when compared with number of years between first exposure and death. Also when colorectal cancers were examined for only those workers with the "highest" exposure levels, the group with the more "intense" exposure had a lower, although significant, increased incidence of colorectal cancers than the overall ethyl acrylate/methyl methacrylate exposed population. According to the author, the excess risk of colorectal cancer did not fit the pattern that would be expected if monomer exposure were actually causing the excess and the excess was biologically difficult to explain. The validity of such a conclusion can be questioned because of absence of exact exposure data, smaller cohort (lack of statistical power) and flawed study design.

Since no clear causal relationship between ethyl acrylate/methyl methacrylate and increased relative risk of colorectal cancer was established, Rohm and Haas (1986a,b) conducted further analyses and studies among Bristol plant hourly employees hired after 1945 and among workers at the Knoxville,

TN plant. The mortality rates among Bristol plant employees hired after 1945 were examined for all white males from January 1946 through December 31, 1982. A total of 6667 men (4035 hourly, 2632 salaried) were included in the study population. As in earlier studies, expected deaths were calculated from mortality rates among U.S. white males. Although potential for exposure to ethyl acrylate was present in the jobs examined, it was considered to be minor exposure relative to methyl methacrylate that constituted the major occupational exposure in all ethyl acrylate/methyl methacrylate workers from 1933-1982. Vital status was verified for 91% of the 6667 white males, status of remaining 9% unknown; 701 deaths were identified (821 expected, SMR=85). Among those deaths from cancers, no significant excess of site-specific cancers occurred. No cases of rectal cancer were found and cancers of the large intestine were similar in number to those expected (13 observed vs. 13.2 expected). When salaried employees were excluded from analysis, the cancer incidence of the 4035 hourly employees was very similar to that reported for the whole plant population. No specific cancer site was significantly elevated and deaths from all cancers were equivalent to predicted values (110 observed vs. 107.8 predicted). Among hourly employees 65.5% (2644) held jobs that involved potential exposure to ethyl acrylate/methyl methacrylate, 60% had a >20-year latency period from first exposure. Deaths from cancer were equivalent to expected values (73 vs. 72.2); 6 colorectal cancers were observed versus 7.7 expected. Relative risk of colorectal cancer did not increase with increasing exposure to ethyl acrylate/methyl methacrylate, whether exposure was assessed as a cumulative "dose" or simply as length of time exposed, although Mantel (1986) criticized the methodology used to establish "dose". This is discussed later.

A similar separate study was conducted at the Knoxville plant (Rohm and Haas, 1986b). The study population included all white males (3381) employed during the period January 1, 1943 through December 31, 1982. Vital status for 91% of the 3381 white male employees was verified, status of remaining 9% was listed as unknown. Overall deaths from all causes were 858, 175 of which were cancer related. Cancers of the digestive tract including colorectal cancers were significantly lower than that predicted (28 observed vs. 51.6 expected). Respiratory cancer mortality rates were significantly elevated when compared with U.S. men (87 vs.63.3; SMR=167); however, when the standard mortality rate among employees was compared with the SMR for respiratory cancer for white males in Knox County, TN, the SMR was still elevated but somewhat reduced (87 vs. 78.8; SMR=110). When salaried employees were excluded from analysis, mortality rates among hourly employees whether analyzed by cumulative exposure or by years exposed on the job, showed no increased risk of cancer at any site. Colorectal cancers were not elevated (9 vs. 16.6). A total of 1271 white males held jobs that were judged to involve potential exposure to polymer particulates. No association was found between cumulative exposure "dose" and risk of respiratory cancer or digestive cancers including colorectal cancers. Workers were assessed in groups of <10, 10-19 and 20+ years from first exposure.

Rohm and Haas (1986a,b) summarized their findings of the four epidemiology studies as follows:

1. The 1933-1945 Bristol plant study found that cancers of the colon and rectum were significantly higher than expected among hourly employees who had worked for at least 1 year in acrylate/methacrylate operations.

2. The excess of colorectal cancers found among employees with primarily mixed exposures to methyl methacrylate and low levels of ethyl acrylate did not fit the pattern that would be expected if monomer exposure were actually causing the excess.

3. A mortality study of 1372 hourly employees at the Deer Park, TX plant (1948-1977) found no signs of digestive cancer among employees handling ethyl acrylate/methyl methacrylate monomers but exposures in this plant were much lower than those at the Bristol plant.

4. Contrary to the findings at the Bristol plant for workers hired before 1946, workers hired after 1945 and followed through December 1982 at the same site, the number of cancers of the large intestine and rectum was not greater than expected (reduced exposure and less latency).

5. A separate study of similar processes at the Knoxville plant from 1943-1982, that included heavier production exposures as well as lower recent exposures than those present at the Bristol plant, found no excess of colorectal cancers among ethyl acrylate/methyl methacrylate workers and no association of these cancers with either monomer vapor or polymer particulates. The explanation for the presence of an excess of cancers of the colon and rectum in ethyl acrylate/methyl methacrylate workers hired before 1945 and the absences of an excess among those hired later is not clear. Latent periods of <10, 10-19 and 20+ years from first exposure were used.

Rohm and Haas (1986a) concluded from these studies that no convincing cause for the colorectum cancers was found in the earlier group and the observations do not support an association between ethyl acrylate or methacrylate exposure and an increased incidence of colorectal cancers. The problems of the Knoxville and Deer Park plant studies can be summarized as follows: lower exposure, shorter duration in follow-up, ill-defined nosology, "death due to ill defined causes", and finally, lack of consistency. Cohorts in different plants did not disprove a positive finding.

In a review of the Rohm and Haas (1984) cohort mortality study, Mantel (1986) has pointed out several weaknesses in the design of this study and the analyses performed and questions the validity of the Rohm and Haas conclusions. Mantel (1986) found that exposure to ethyl acrylate or methyl methacrylate was not scored in any specific fashion. Attention was focused on comparison with external controls either the general U.S. white male population or regional males (Pennsylvania and New Jersey), disregarding internal data. The Rohm and Haas study showed certain SMRs for the entire

plant and for employees ever in ethyl acrylate/methyl methacrylate-related jobs; this tended to reflect a healthy-worker bias (if adjustment had been made for latent factors, this could be eliminated) and therefore these ratios are characteristically below unity. Mantel (1986) also pointed out that when comparisons are made using workers with at least 1 year of employment an SMR=210 was obtained by Rohm and Haas for latency of at least 10 years. However, by diffencing this population by exposure and duration, Mantel (1986) derived an SMR=312. While the Rohm and Haas study does take into account accumulative exposure to workers, the duration of exposure was not kept constant over the dosing period thereby diluting any dose-response effect. Mantel also pointed out that the lack of dose-response effect indicated by the decrease in SMRs with increasing latency periods is an artifact of the design because of increasing background rates. If in fact age cutoffs are used in analyzing this data, SMR ratios increase. Mantel concluded that the data in the Rohm and Haas (1984) study has shown that occupational exposure to ethyl acrylate/methyl methacrylate increased the relative risk of colorectal cancer among workers 3-fold.

5.2. MUTAGENICITY

Ethyl acrylate was found not to be mutagenic in plate incorporation assays (Table 5-5) of Salmonella typhimurium strains TA98, TA100, TA1537 or TA1538 (NTP, 1986a; Haworth et al., 1983; Waegemakers and Bensink, 1984). Results were the same with or without metabolic activation. Ishidate et al. (1981) detected chromosomal aberrations in 20% of all metaphases of a lung fibroblast culture from Chinese hamsters at a dose of 9.8 µg/mℓ ethyl acrylate in the absence of S-9. An increased incidence of mutations at the thymidine kinase locus in a mouse lymphoma assay was reported by Litton Bionetics (1980), after treatment of cells with cytolethal doses of ethyl

TABLE 5-5

Mutagenicity Testing of Ethyl Acrylate

Assay	Indicator/ Organism	Compound and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurim TA98, TA100, TA1535, TA1537	99.7% pure in DMSO or H_2O	plate incorporation	33-10,000 µg/plate	±S-9	-	Both rat liver and hamster liver S-9 used	Haworth et al., 1983; NTP, 1986a
Reverse mutation	S. typhimurim TA98, TA100, TA1535, TA1537 TA1538	>99% in DMSO	plate incorporation	30-2000 µg/plate	±S-9	-	NC	Waegemaekers and Bensink, 1984
Chromosomal aberration	CHL cells, lung fibroblast line	NR	liquid suspenion	9.8 µg/mL	none	+	Dose at which chromosomal aberrations were detected in 20% of metaphases	Ishidate et al., 1981
Forward mutation	L51784 mouse lymphoma cells	dissolved in DMSO	liquid suspension	0.195-100 nL/mL	±S-9	+ +	Increase in mutations began at 30 µg/L (-S-9) and 100-150 µg/L (+S-9)	Litton Bionetics, 1980
Mouse micronucleus test	male Balb/C mice	dissolved in distilled water	intraperitoneal injection	112.5-1800 mg/kg	NA	+	Dose-related increases in polychromatic erythrocytes with micronuclei at doses lethal to some polychromatic cells	Przybojewska et al., 1984

NR = Not reported; NA = not applicable; NC = no comment

acrylate. The response was reduced in the presence of S-9. Przybojewska et al. (1984) injected groups of male Balb/c mice with 112.5-1800 mg/kg intraperitoneal ethyl acrylate and subsequently removed the femurs of the treated mice for analysis of polychromatic micronuclei. They found that ethyl acrylate, which exerted a dose-related increase in polychromatic lethality, also effected a dose-related increase in micronuclei.

5.3. TERATOGENICITY

Murray et al. (1981) exposed groups of 33 gravid Sprague-Dawley rats to 0, 50 or 150 ppm (205 or 614 mg/m^3) ethyl acrylate vapor, 6 hours/day, on days 6-15 of gestation. Maternal rats were observed daily for toxic symptoms; food and water consumption was measured every 3 days beginning on gestation day 6, and maternal body weights were recorded 7 times during gestation. On day 21, the pups were removed by Caesarean section, the dams were sacrificed and their livers weighed. Investigators recorded the position and number of live, dead and resorbed fetuses, and the uteri of nonpregnant rats were stained for examination of early resorption sites. Each fetus was weighed and sexed and the crown-rump length was measured. One-third of the fetuses in each litter was examined microscopically for soft tissue anomalies, and all fetuses were cleaned and stained with alizarin red-S for analysis of skeletal abnormalities.

Except for the initial measurement on day 6, dams exposed to 150 ppm weighed significantly less than controls throughout the exposure period and on days 16 and 18. Most of the weight gain inhibition of high-dose females occurred on gestation days 6 and 7. During exposure, the total amount of weight gained was decreased by 48% in the high-dose group, which also had a significant decrease in food consumption and a significant increase in water

consumption. There were no changes in absolute or relative liver weights at either exposure level, and there were no exposure-related effects on parameters of maternal reproductive performance or on nonteratogenic manifestations of fetal toxicity.

When the litter was considered as the unit of analysis, the incidences of major malformations in the offspring of treated dams were not significantly different from control rats (Fisher exact p=0.10 by an independent analysis done at SRC), although the incidence of fetuses with hypoplastic tails was higher than historical controls. Three of 338 fetuses from 3/29 litters of dams exposed to 150 ppm had multiple occurrences of major malformations. The first had a short trunk, hypoplastic tail, small anal orifice, ectopic ovaries, missing ribs, vertebrae and centra, and fused and malformed ribs. The second fetus showed a hypoplastic tail, small anal orifice and missing vertebrae and the third had a hypoplastic tail and missing vertebrae. The significant decrease in maternal weight at the high dose makes the interpretation of these effects difficult. None of the control or 50 ppm fetuses was found to have a major malformation.

Gravid rats treated by an unspecified route with 25-400 mg/kg ethyl acrylate from 7-16 days of gestation had decreased body and placental weight gains and increased numbers of resorptions (Pietrowicz et al., 1980). The size and number of live fetuses were not affected by treatment, but the investigators noted increased numbers of skeletal anomalies in the offspring of exposed rats. No further details were available and therefore no conclusions from theis data can be made.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the other reproductive effects of ethyl acrylate could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

The NTP (1986b) is currently preparing the final technical report of a lifetime exposure study of B6C3F1 mice and F344 rats. In the 2-year study, groups of 50 male and 50 female rats and 50 male and 50 female mice were given gavage doses of 0, 100 or 200 mg/kg ethyl acrylate in corn oil, 5 days/week for 103 weeks. All rats and mice were observed twice daily for morbidity and mortality; body weights were recorded weekly for 12 weeks and monthly thereafter. Gross necropsies were performed on all rats and mice found dead and on those sacrificed at the end of the study. Major tissues were examined for grossly visible lesions. Histopathological analysis of gross lesions, abnormal lymph nodes, tissue masses and 33-34 other sites was conducted on nonautolyzed rats and mice of all dose groups.

There were no treatment-related effects upon survival in either rats or mice, or upon growth in either sex of rats. Body weights of male mice were also unaffected by treatment. Administration of 100 mg/kg to female mice led to an inhibition in growth, particularly in the latter half of the study; however, a similar inhibition in growth rate was not found in the high-dose females.

Prominent in both species were dose-related increased incidences of forestomach lesions, characterized by inflammation, epithelial hyperplasia and hyperkeratosis. Ulceration was dose-related in mice. Hairballs and accompanying inflammatory reactions were sometimes found in the mucosa of rats.

Two-year studies using dogs and rats given oral ethyl acrylate were conducted by Borzelleca et al. (1964). Groups of 25 male and 25 female Wistar rats were initially given either 0, 6, 60 or 2000 ppm ethyl acrylate in

drinking water. During the fifth month, the 6 and 60 ppm levels were raised to 7 and 70 ppm. Polarographic analysis of independent samples of treated water revealed only marginal loss of acrylate monomer.

Food and fluid consumptions were evaluated periodically. At 3-month intervals, hematocrit, hemoglobin and total white and differential cell counts were measured on five rats/sex in each treatment group. Semi-quantitative urinalyses for reducing substances and protein were performed at 3-month intervals from five rats/sex/treatment group. Upon terminal sacrifice at 2 years, organ-to-body weight ratios of the heart, spleen, kidney, liver and testes were measured. Histopathological analysis of 16 major tissue sites was also performed.

Borzelleca et al. (1964) found no differences in survival rates that were due to treatment. Administration of the 2000 ppm level significantly ($p<0.05$) depressed body weight gain in both sexes during the first year and continued to depress female body weight gain in the second year. This level also significantly decreased overall fluid consumption in both sexes of rats and decreased food consumption in females. There were no treatment-related effects on hematological, urinary or histopathological parameters or on relative organ-to-body weight ratios.

In the chronic dog study, Borzelleca et al. (1964) administered ethyl acrylate dissolved in corn oil by gelatin capsules. Preliminary investigations revealed a dissolution rate of $\leq$5% after 5 days. Groups of two male and two female beagles were given doses equivalent to dietary concentrations of 0, 10, 100 or 1000 ppm ethyl acrylate. Dogs receiving 10 or 100 ppm tolerated administration well; however, all four dogs given 1000 ppm vomited. Starting on the second week, these dogs tolerated 300 ppm daily;

this level was raised to 400 ppm at 5 weeks, to 500 ppm at 7 weeks, to 600 ppm at 9 weeks, to 700 ppm at 12 weeks, to 800 ppm at 14 weeks and finally to 1000 ppm at 16 weeks. The 1000 ppm level was maintained for the duration of the study. Thus, the TWA was 931 ppm.

Hematological tests and urinalyses were performed before dietary administration, at 2, 4 and 13 weeks after administration, and at 13-week intervals thereafter. At sacrifice, organ-to-body weight ratios were calculated and histopathological studies were made on all tissues. Slight decreases in body weight gain, correlated with decreased food consumption in the high-dose dogs, were the only treatment-related effects observed.

The NTP (1986a) conducted 13-week studies of ethyl acrylate administration using F344 rats and B6C3F1 mice. Groups of 10 female and 10 male rats were administered ethyl acrylate in corn oil by gavage, 5 times/week at dose levels of 0, 7, 14, 28, 55 or 110 mg/kg. Groups of 10 mice/sex were administered ethyl acrylate in corn oil by gavage, 5 times/week at dose levels of 0, 1.5, 3, 6, 12 or 25 mg/kg. In a second study, 10 male and 10 female mice/dose group received 0, 12, 25, 50 or 100 mg/kg ethyl acrylate in corn oil on the same treatment schedule. All rats and mice were checked for mortality and morbidity twice daily; those found moribund were sacrificed and necropsied. Each rat or mouse was clinically examined weekly, and body weight measurements were taken. At sacrifice, rats and mice were necropsied. In the control and high-dose groups only, 29 tissues were examined histologically; no histological examinations were performed on mice and rats from other dose groups.

Treatment had no effect on the longevity or body weight gain of rats. There were no compound-related clinical signs or evidences of histopathological changes, except for an occasional reddened duodenum or prominent

vasculature in the stomachs of male rats receiving 110 mg/kg. In the first subchronic mouse study, 2/10 females receiving 25 mg/kg and 1/10 females receiving 6 mg/kg died during the exposure period. The cause of death in these mice was unclear. Mean body weight gains were not affected by treatment. In the second mouse study, there were no dose-related affects on body weights or mortality rates. No evidence of gross or microscopic tissue damage from compound administration was apparent in either mouse study.

Treon et al. (1949) orally dosed two rabbits with 31.5 mg/kg ethyl acrylate, 5 days/week for 7 weeks. Besides a small inhibition in growth rate, no overt signs of toxicity were observed. The rabbits were sacrificed 2 months after administration of the last dose, at which time there were no gross or microscopic changes in examined tissues.

Miller et al. (1985) exposed F344 rats and B6C3F1 mice of both sexes by inhalation to 0, 25, 75 or 225 ppm (0, 102, 307 or 921 mg/m^3) ethyl acrylate, 6 hours/day, 5 days/week (excluding holidays) for up to 27 months. Initially, there were 92 rats/sex in each of the two control groups and 115 rats/sex in each of the three treatment groups. There were also 84 mice/sex in each of the two control groups and 105 mice/sex in each exposure group. Eight rats/sex in each control group and 10 rats/sex in each exposure group were sacrificed after 3, 6, 12 or 18 months of exposure; 8 mice/sex/control group and 10 mice/sex/exposure group were sacrificed after 6, 12, or 18 months of exposure. Based upon interim results, the high-dose rats and mice were withdrawn from exposure after 6 months and maintained for an additional 21 months.

All groups of rats and mice were observed daily for manifestations of toxicity. Body weights were measured weekly for the first 3 months, biweekly during months 4-6 and monthly thereafter. Moribund rats and mice

were sacrificed and histopathology on nonautolyzed tissue was collected for hematological (erythrocyte counts, PCV, hemoglobin concentration, total and differential leukocyte counts) and blood biochemical (alkaline phosphatase and SGPT activities, BUN, and glucose) assessments. Rats only were also analyzed for cholesterol, fasting blood sugar, triglycerides, total protein, albuminum and globulins. Urinalyses on rats evaluated urobilinogen, bilirubin, glucose, ketones, blood, pH, protein and specific gravity. Statistical analyses of organ weights, clinical chemistry and hematology data were not performed for the rats and mice sacrificed at 27 months, because of the high incidence of spontaneous diseases found in aging animals. At terminal sacrifice (27 months), the liver, kidney and brain weights were recorded for mice and the liver, kidney, brain, heart, spleen and testes weights for rats. Approximately 50 tissues were taken from each rat or mouse for gross and histological examination in the control and 75 ppm groups; in the 25 and 225 ppm groups, ~15 tissues were examined histologically.

No effects on mortality rates were found in rats. There were immediate and lasting inhibitions in body weight gain in the 75 and 225 ppm groups, although the degree of inhibition was diminished in the latter group after exposure ended. Relative brain, liver and kidney weights of subgroups of rats serially sacrificed (up to and including 27 months of exposure) were unremarkable. Histopathological examination of tissues from rats maintained in the chronic study revealed treatment-related nonneoplastic lesions of the olfactory portions of the nasal cavity. Concentration-related increases in severity and incidence of basal cell hyperplasia, intraepithelial glands, "respiratory metaplasia" and multifocal mineralization were found in rats of

both sexes exposed to 25 or 75 ppm. Diffuse atrophy of the olfactory epithelium was confined almost exclusively to the 225 ppm group. At 25 ppm, the primary manifestation was a decrease in the number of mature neurons in the mucosa, with compensatory hyperplasia, stratification of basal cells and an increase in intraepithelial glandular elements. In 16 males and 6 females, there was slight to moderate "respiratory metaplasia," or replacement of the olfactory epithelium with a ciliated respiratory epithelium similar to that lining the upper respiratory tract. At 75 ppm, lesions were similar but more extensive in terms of both incidence and the extent of nasal cavity affected. Virtually all rats exposed to this concentration had respiratory metaplasia and multifocal mineralization of the olfactory epithelium. At 225 ppm, diffuse atrophy was characterized by a diminished epithelium consisting of a single layer of support cells and a single layer of focally hyperplastic basal cells. Incidences of other lesions, including increased intraepithelial glandular elements, respiratory metaplasia and mineralization, were intermittent among those of the 25 and 75 ppm groups.

The only other treatment-related pathological change considered by the investigators to be of biological significance was a positive concentration-related trend in males, in the incidences of foci of adrenal medullary hyperplasia. Since these lesions are precursors of medullary neoplasia, and the number of rats in the 25 and 75 ppm groups that had adrenal neoplasia was less than the number of similarly afflicted control rats, Miller et al. (1985) concluded that fewer of the proliferative adrenal lesions in the exposed rats had progressed to the oncogenic stage.

Longevity of mice was not adversely affected by any treatment concentration. Mean body weight gains in the 75 and 225 ppm mice of both sexes were significantly lower than for control groups. Near the end of the study,

body weight gains in the 25 ppm mice were also slightly depressed. Relative brain, liver and kidney weights of subgroups of mice serially sacrificed (up to and including 27 months) were unremarkable. No adverse effects on hematology, clinical chemistries or urinalyses on subgroups of mice sacrificed after 6, 12, 18 or 27 months of exposure were noted. Pathologically, exposure-related lesions in treated mice were restricted to the nasal mucosa. Concentration-related increases in the incidences of submucosal hyperplasia and respiratory metaplasia were found in both males and females. In mice exposed to 225 ppm for 6 months and sacrificed at 27 months, the extent of area affected, but not the severity of lesion, increased. No other exposure-related gross or microscopic changes were observed in any tissues of mice.

In rats exposed to 25 ppm (102 mg/m^3) and sacrificed after 6 or 12 exposure months, there was very slight focal degeneration of the olfactory epithelium and very slight inflammation of the nasal mucosa and submucosa (Miller et al., 1979a). After exposure to 75 ppm for 6 or 12 months, rats had slight focal hyperplasia of the basal cells, slight to moderate focal degeneration of the olfactory epithelium and occasional infolding of the mucosal surface. The chief difference between 6 and 12 months exposure was the extent of area affected. In separate groups of 10 rats/sex exposed to 225 ppm for 6 months and sacrificed 3 or 6 months later, there was evidence of healing and recovery of olfactory lesions.

Miller et al. (1985) also chronically exposed rats and mice to 5 ppm (20 mg/m^3) ethyl acrylate, 6 hours/day, 5 days/week for 24 months for determination of a no-effect level for histopathological changes. Eighty rats and 80 mice of each sex served as controls and 90 rats and 90 mice of each sex were in the treated groups. Subgroups of rats and mice were sacrificed

after 6, 12, 18 and 24 months of exposure for analysis of nasal turbinate lesions only. The investigators observed no neoplastic or nonneoplastic changes at this concentration and treatment did not affect either mortality or clinical appearances of rats and mice.

As cited by U.S. EPA (1981), 10 B6C3F1 mice and 10 F344 rats of each sex were exposed 6 hours/day, 5 days/week to ethyl acrylate vapor at concentrations of 0, 75, 150 or 300 ppm (0, 307, 614 or 1228 mg/m^3) for 22 days (Miller et al., 1979b). The rats and mice were observed daily for signs of toxicity and were examined for gross pathological lesions. Selected organs were examined microscopically. At 300 ppm, the mean weight gains of male rats, male mice and female rats were significantly less than those of controls. At 150 ppm, the mean body weight gain among male and female rats was also significantly reduced, relative to controls. Mean kidney-to-body weight ratios were significantly increased in the 300 ppm rats of both sexes and in the 150 ppm females. In addition, the absolute and relative liver weights of mice of both sexes exposed to the two highest concentrations were significantly lower than control weights. The only histopathological effect involved lesions of the nasal turbinate in male mice and rats exposed to the high concentrations. The effect involving principally the dorsomedial olfactory epithelium was characterized by inflammation, degeneration, focal necrosis and squamous metaplasia.

Pozzani et al. (1949) exposed groups of 15 male and 15 female Sherman rats and 8 or 9 albino male rabbits by inhalation to 0, 70 or 300 ppm (0, 287 or 1228 mg/m^3), 7 hours/day, 5 days/week for 30 days. Histological examinations were performed on the liver, kidney, heart, lung, pancreas, spleen and adrenal. At 300 ppm, 18/30 rats died before the end of the study

and had pneumonic and cloudy swelling of renal tubules and liver. The 300 ppm group rats that survived had decreased body weight gain and increased kidney weights, and 3/12 had minor liver or lung lesions. The only effect at 70 ppm in rats was increased kidney weights of males. At 300 ppm, all 9 rabbits died within 7 days and at 70 ppm, 2/8 died within 30 days compared with 3/8 controls. Pulmonary infection was thought to be the cause of death.

Treon et al. (1949) observed no effects on rabbits, guinea pigs, rats or monkeys exposed to ethyl acrylate 7 hours/day at 99 or 105 mg/m³ for 62-130 times over 199 days, or to 300 mg/m³, 50 times over 72 days. Two rats, two guinea pigs and one monkey exposed for 28 days to 1090 mg/m³ showed large weight losses and signs of respiratory irritation, conjunctivitis, lethargy and diarrhea. One guinea pig died as a result of exposure; four similarly exposed rabbits died within 8-17 days of the start of exposure. Surviving animals removed from the chamber were prostate, ataxic, convulsive, had opisthotonos, and had breathing difficulties indicative of pulmonary edema. Gross and microscopic examination of poisoned animals revealed brain, spleen, kidney, lung and liver congestion, dilation of cardiac chambers, myocardial degenerations, fatty hepatic changes, edema, pyknosis and karyolysis. No significant changes were found in the tissues of animals that survived exposure and were sacrificed 2 months later.

5.6. OTHER RELEVANT INFORMATION

Oral LD_{50} values for ethyl acrylate of 1.797 g/kg in male ddY mice (Tanii and Hashimato, 1982), 1.02 g/kg in male albino rabbits (Pozzani et al., 1949) and ~0.35 g/kg in female rabbits (Treon et al., 1949) have been reported. The NTP (1986a) conducted three 14-day oral studies of ethyl acrylate in F344 rats and B6C3F1 mice of both sexes. In the first study,

administration of 110, 225 or 450 mg/kg ethyl acrylate in ethanol led to thickened forestomach mucosa in rats; after 450 mg/kg adhesion of the spleen and stomach to the peritoneum occurred. A dose of 900 mg/kg was fatal to all rats within 24 hours. In mice, the 450 mg/kg dose led to a thickened, rough mucosal surface in the forestomach and for both males and females, 1/5 mice died shortly after termination of exposure. The dose of 450 mg/kg was the highest one used; the NTP (1986a) did not discuss histopathological changes at lower doses. In the second study, ethyl acrylate was administered in drinking water at concentrations of 0.025-0.45% (rats) and 0.013-0.22% (mice). The only pathological change noted in rats and mice sacrificed after exposure was a reddening of the duodenal mucosal surface. Because of the stability of ethyl acrylate in water, faulty sipping tubes, broken water bottles and spillage, this method of administration was considered inappropriate for further testing. Finally, in the third 14-day study, groups of five rats and mice of each sex were administered 0, 100, 200, 400, 600 or 800 mg/kg ethyl acrylate in corn oil daily for 14 consecutive days. Histological examinations were made of the stomachs of rats administered 0-400 mg/kg and of mice given 0-600 mg/kg. In rats, abdominal adhesions and a thickened stomach wall were observed beginning at 100 mg/kg. Starting at 400 mg/kg, ulcerative and nonulcerative forestomach inflammation, characterized by the presence of neutrophils, lymphocytes and histiocytes in the mucosa and submucosa, were observed. The forestomachs of most mice receiving 200-800 mg/kg were grossly thickened and abdominal lesions were observed at the high dose. Nonulcerative inflammation was first observed at 200 mg/kg and more severe ulcerative lesions were first seen at 400 mg/kg. Administration of up to 800 mg/kg for 14 days did not kill any of the treated rats or mice.

Ghanayem et al. (1985a) studied the dose-response relationship, time course and effect of route of administration of ethyl acrylate upon the stomachs of rats. In male F344 rats dosed singly with 100, 200 or 400 mg/kg ethyl acrylate in corn oil, there was a dose-related increase in mucosal congestion and submucosal edema of both the glandular and forestomach, as well as vacuolization of the tunica muscularis. In rats orally dosed with 200 mg/kg ethyl acrylate in corn oil and sacrificed 2, 4, 8 or 24 hours after administration, the occurrences and severity of lesions of the forestomach increased with time. The incidences of submucosal edema and inflammation were also positively related to time after administration. Whereas a subcutaneous dose of 200 mg/kg ethyl acrylate was without effect on stomach histology, intraperitoneal administration of the same dose led to microscopic submucosal edema and vacuolization of the tunica muscularis of the forestomach. The congestion and edema observed after intraperitoneal administration, however, were of considerably less severity than gastric signs of toxicity after oral dosing. Administration of four consecutive oral doses of 200 mg/kg ethyl acrylate increased the incidences of superficial mucosal necrosis of the glandular stomach, as well as erosions, mucosal hyperplasia and vacuolization of the tunica muscularis of the forestomach, relative to a single administration. Ghanayem et al. (1985a) concluded that ethyl acrylate caused an immediate inflammatory response, typical of irritants, which were more pronounced in the forestomach than in the glandular stomach.

In a follow-up study, Ghanayen et al. (1985b) explored the parameters responsible for ethyl acrylate-induced gastric edema. Using a series of three acrylate esters (methyl, ethyl and butyl), Ghanayem et al. (1985b)

demonstrated that the extent of forestomach edema as measured gravimetrically was positively correlated with concentration of ester in the vehicle and polarity of the vehicle and negatively correlated with alkyl chain length. Equimolar dosing with acrylic acid, ethyl and methyl methacrylates or the fully saturated ethyl and methyl propionate failed to induce edema. As in the previous study, effects on the glandular stomach were not as pronounced as were those on the forestomach.

Lomonova and Klimova (1979) calculated LC_{50}s of 16,200 and 7500 mg/m³ for unspecified durations for mice and rats, respectively, exposed by inhalation to ethyl acrylate vapors. Inhalation of 2010 mg/m³ ethyl acrylate, 7 hours/day, was lethal to all exposed rabbits in 4 days and all exposed rats and guinea pigs in 13 days (Treon et al., 1949). Similarly, inhalation exposure of 4830 mg/m³ for 7 hours/day was lethal in 1-2.2 days to four rabbits, two guinea pigs, two rats and one monkey.

After dermal application of ethyl acrylate, the skin of rabbits was edematous, necrotic and erythematous (Pozzani et al., 1949; Treon et al., 1949). Treon et al. (1949) noted scattered collections of polymorphonuclear leukocytes, focal abscesses and complete destruction of the epidermis. Application of 0.5 mℓ of the undiluted ester to the corneas of rabbits produced severe necrosis in 24 hours, whereas 0.1 mℓ led to a mild necrosis (Pozzani et al., 1949). Application of 23 mg ethyl acrylate to the shaved backs of C3H/HCJ mice 3 times/week for life led to no gross lesions (DePass et al., 1984). Microscopically, the treated skin appeared necrotic and fibrotic, and the mice had dermatitis and hyperkeratosis.

5.7. SUMMARY

An NTP (1986a) report of the potential carcinogenicity of ethyl acrylate after oral (gavage) administration in F344 rats and B6C3F1 mice of both sexes indicated that ethyl acrylate induced squamous cell carcinomas or

papillomas (or both) of the forestomach in both species. For both species, dose levels were 0, 100 and 200 mg/kg, 5 days/week for 103 weeks.

No evidence of carcinogenicity was found in rats given up to 2000 ppm in the drinking water for 2 years (Borzelleca et al., 1964).

Miller et al. (1985) found no evidence of carcinogenicity in B6C3F1 mice and F344 rats exposed by inhalation to up to 75 ppm (307 mg/m^3) ethyl acrylate, 6 hours/day, 5 days/week, for 27 months, or in rats and mice exposed to 225 ppm (921 mg/m^3), 6 hours/day, 5 days/week for only 6 months, then maintained for 21 months until terminal sacrifice.

DePass et al. (1984) found no increase in epidermal tumor incidence in C3H/Hej male mice skin-painted with 23 mg/mouse ethyl acrylate, 3 times/week for 2 years.

A causal relationship for increased incidences of cancer of the colon and rectum from occupational exposure to ethyl acrylate/methyl methacrylate was suggested in a retrospective epidemiology study on workers employed at the Bristol, PA plant before 1946; however, the causal relationship could not be fully established when relative accumulated total exposure and latency were considered (Rohm and Haas Co., 1984). Further analyses and studies were conducted at the above plastic manufacturing facility for employees hired after 1946. In these studies no incidences of cancer of the colon and rectum were found (Rohm and Haas, 1986a). Similar studies conducted at manufacturing sites in Texas and Knoxville, TN, found no signs of increased digestive cancers including colorectal cancers among hourly employees (Rohm and Haas, 1981, 1986b). A review of the Rohm and Haas (1984) study has pointed out several weaknesses in the study design and analyses perfomed that may have diluted the dose-response effect reported by

Rohm and Haas (1984) and suggests that a causal relationship between ethyl acrylate/methyl methacrylate exposure and increased incidences of colorectal cancers does exist (Mantel, 1986).

Ethyl acrylate has been found to be nonmutagenic in standard reverse mutation assays with and without metabolic activation (NTP, 1986a; Haworth et al., 1983; Waegemakers and Bensink, 1984). Principally at cytolethal doses, ethyl acrylate was mutagenic to CHL cells (Ishidate et al., 1981) and mouse lymphoma cells (Litton Bionetics, 1980) in culture. Przybojewska et al. (1984) demonstrated genotoxicity of ethyl acrylate in the micronucleus test using Balb/c mice.

Murray et al. (1981) demonstrated that exposure of rat dams to 50 or 150 ppm (205 or 614 mg/m^3) ethyl acrylate, 6 hours/day, from days 6-15 of gestation, had no effect upon reproductive performance in dams although weight gain was significantly inhibited at the high concentration. There were no fetal malformations at 0 or 50 ppm. At 150 ppm, pups from 3/29 treated litters had multiple (primarily skeletal) malformations. Although this incidence was not statistically different from control rats, in a second reproductive study, Pietrowicz et al. (1980) stated that treatment of rat dams by an unspecified route with 25-400 mg/kg ethyl acrylate during gestation was associated with decreased body and placental weight gains, increased numbers of resorptions and skeletal abnormalities.

In the 2-year gavage study by NTP (1986a), rats and mice had dose-related increases in forestomach hyperplasia, hyperkeratosis, inflammation or ulceration at $\geq$100 mg/kg, 5 days/week. The only effect in rats treated with ethyl acrylate in the drinking water at concentrations up to 2000 ppm or dogs treated orally by capsule with up to ~931 ppm (TWA) was decreased body weight gain in high-dose female rats (Borzelleca et al., 1964).

In F344 rats given 0-110 mg/kg ethyl acrylate by gavage 5 times/week for 13 weeks, there were no treatment-related effects on body weight gain, longevity or clinical signs (NTP, 1986a). The only prominent histopathological change, occurring in the high-dose males, was an occasional reddened duodenum or pronounced stomach vasculature. Administration of up to 100 mg/kg ethyl acrylate to male and female B6C3F1 mice on the same treatment schedule had no effects on longevity, body weight gain or gross or microscopic histopathology (NTP, 1986a). Similar results were obtained by Treon et al. (1949) in two rabbits given 31.5 mg/kg ethyl acrylate orally, 5 times/week for 7 weeks. In a series of 14-day oral studies, the NTP (1986a) determined that gavage administration of 100 mg/kg/day ethyl acrylate in rats and 200 mg/kg/day ethyl acrylate in mice led to abdominal adhesions, thickened forestomach mucosa and nonulcerative inflammation. Administration of higher doses resulted in ulcers and more severe inflammation. Oral LD_{50} values ranging from 0.35-1.8 g/kg have been reported (Tanii and Hashimoto, 1982; Pozzani et al., 1949; Treon et al., 1949).

In the chronic inhalation study, nonneoplastic lesions of the nasal mucosa (e.g., hyperplasia, mineralization, inflammation, metaplasia) occurred in mice and rats at exposures $\geq$25 ppm ($\geq$102 mg/m^3), 6 hours/day, 5 days/week for up to 27 months (Miller et al., 1985). Exposure to 5 ppm, 6 hours/day, 5 days/week had no effect.

Inhalation exposure to lethal concentrations (1090 mg/m^3, 7 hours/day for 28 days) of ethyl acrylate led to weight loss and severe signs of mucosal irritation in rats, guinea pigs, rabbits and in one monkey (Treon et al., 1949); these signs included conjunctivitis, lethargy and diarrhea. Examination of poisoned rats, guinea pigs and rabbits revealed multiorgan

involvement and a variety of edematous and degenerative changes. These changes were found to be reversible in survivors that were sacrificed 2 months after termination of exposure. Exposure at 70 ppm (287 mg/m³) for 7 hours/day in rabbits, guinea pigs, rats and monkeys was without adverse effects (Pozzani et al., 1949; Treon et al., 1949). Lomonova and Klimova (1979) determined LC_{50s} of 16,200 and 7500 mg/m³ for unspecified durations for mice and rats, respectively.

Ethyl acrylate is a potent skin irritant (Pozzani et al., 1949; Treon et al., 1949) inducing erythema, edema, cellular necrosis and abscesses. Corneal necrosis after ocular application in rabbits was observed by Pozzani et al. (1949).

6. AQUATIC TOXICITY

6.1. ACUTE

Little information is available concerning effects of ethyl acrylate on aquatic organisms. Hermens and Leeuwangh (1982) determined a 14-day LC_{50} of 7.4 µmol/ℓ (0.74 mg/ℓ) for guppies, Poecilia reticulata. Price et al. (1974) reported a 24-hour LC_{50} of 12 mg/ℓ for brine shrimp, Artemia salina. Paulet and Videl (1975) reported a 3-day LC_{50} of 5 mg/ℓ for an unspecified fish species.

6.2. CHRONIC

Pertinent data regarding chronic toxicity of ethyl acrylate to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data regarding effects of ethyl acrylate on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

Pertinent data regarding residues of ethyl acrylate in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

U.S. EPA (1972) reported that 0.6 mg/ℓ ethyl acrylate was the threshold for tainting of fish flesh.

6.6. SUMMARY

The information concerning toxicity of ethyl acrylate to aquatic biota is very limited. LC_{50} values of 0.74 and 12 mg/ℓ were reported for guppies (Hermens and Leeuwangh, 1982) and brine shrimp (Price et al., 1974), respectively.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1985-1986) has adopted a TLV-TWA of 5 ppm (~20 mg/m³) for ethyl acrylate and has also recommended deletion of the STEL of 25 ppm (~100 mg/m³). A "skin" designation was also adopted because of ethyl acrylate's potent dermal irritation. The current TLV-TWA is based upon inhalation results by Rohm and Haas (1978), indicating that rats and mice exposed to 25 ppm ethyl acrylate vapors 6 hours/day, 5 days/week for 6 months had slight degeneration of the olfactory part of the nasal mucosa (ACGIH, 1986). The ACGIH (1986) supported the decision of several industrial producers to lower the TLV-TWA from 25 to 5 ppm (~20 mg/m³) in order to minimize sensory irritant effects. It also recommended deletion of the STEL until more quantifiable toxicological and industrial hygiene data were made available.

The U.S. FDA (1983) did not affirm ethyl acrylate as a generally recognized as safe indirect human food ingredient. This agency could not find evidence that the ester was used in the manufacture of food-related paper and paperboard products, except as a component of polymers already covered by current and prior food additive regulations.

OSHA (1985) has recommended a PEL of 25 ppm (~100 mg/m³) with an accompanying "skin" designation. The major producers of acrylates including Rohm and Haas, Celenese, Union Carbide and Daw Badische, agreed on an internal TWA concentration of 5 ppm for an 8-hour day in an occupational exposure setting (U.S. EPA, 1981).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of ethyl acrylate could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

An NTP (1986a) report of the potential carcinogenicity of ethyl acrylate after oral (gavage) administration in F344 rats and B6C3F1 mice of both sexes indicated that ethyl acrylate induced squamous cell carcinomas or papillomas (or both) of the forestomach in both species. For both species, dose levels were 0, 100 and 200 mg/kg, 5 days/week for 103 weeks.

No evidence of carcinogenicity was found in rats given up to 2000 ppm in the drinking water for 2 years (Borzelleca et al., 1964).

Miller et al. (1985) found no evidence of carcinogenicity in B6C3F1 mice and F344 rats exposed by inhalation to up to 75 ppm (307 mg/m^3) ethyl acrylate, 6 hours/day, 5 days/week, for 27 months, or in rats and mice exposed to 225 ppm (921 mg/m^3), 6 hours/day, 5 days/week for only 6 months, then maintained for 21 months until terminal sacrifice.

DePass et al. (1984) found no increase in epidermal tumor incidence in C3H/Hej male mice skin-painted with 23 mg/mouse ethyl acrylate, 3 times/week for 2 years.

A series of retrospective epidemiological studies have been conducted by Rohm and Haas (1981, 1984, 1986a,b) for workers occupationally exposed to ethyl acrylate/methyl methacrylate. A causal relationship for increased incidences of cancer of the colon and rectum has been suggested for workers exposed to ethyl acrylate/methyl methylacrylate (Rohm and Haas, 1984). The data as presented by Rohm and Haas (1984) did not fully establish this causal relationship when relative accumulated total exposure and latency, or later studies conducted at the same site and other manufacturing facilities were considered. However, a review by Mantel (1986) has pointed out several weaknesses with the study design and analyses performed in the Rohm and Haas

(1984) cohort study. Further analyses on this data perfomed by Mantel (1986) indicated that a 3-fold increase in colorectal cancer resulted from occupational exposure to ethyl acrylate/methyl methacrylate.

The data provided by the Rohm and Haas (1981, 1984, 1986a,b) studies and the Mantel (1986) report are insufficient to establish a clear causal relationship for increased incidences of cancer of the colon and rectum from occupational exposure to ethyl acrylate/methyl methacrylate. Moreover, the role of ethyl acrylate as the causative agent for these cancers cannot be determined since exposure to ethyl acrylate and methyl methacrylate could not be separated. However, these studies may provide supportive evidence when considered with the positive incidence of squamous cell carcinomas and papillomas in rats and mice exposed to ethyl acrylate (NTP, 1986a).

Ethyl acrylate has been found to be nonmutagenic in standard reverse mutation assays with and without metabolic activation (NTP, 1986a; Haworth et al., 1983; Waegemakers and Bensink, 1984). Principally at cytolethal doses, ethyl acrylate was mutagenic to CHL cells (Ishidate et al., 1981) and mouse lymphoma cells (Litton Bionetics, 1980) in culture. Przybojewska et al. (1984) demonstrated genotoxicity of ethyl acrylate in the micronucleus test using Balb/c mice.

Murray et al. (1981) demonstrated that exposure of rat dams to 50 or 150 ppm (205 or 614 mg/m^3) ethyl acrylate, 6 hours/day, from days 6-15 of gestation, had no effect upon reproductive performance in dams although weight gain was significantly inhibited at the high concentration. There were no fetal malformations at 0 or 50 ppm. At 150 ppm, pups from 3/29 treated litters had multiple (primarily skeletal) malformations. Although this incidence was not statistically different from control rats, in a second reproductive study, Pietrowicz et al. (1980) stated that treatment of

rat dams by an unspecified route with 25-400 mg/kg ethyl acrylate during gestation was associated with decreased body and placental weight gains, increased numbers of resorptions and skeletal abnormalities.

In the 2-year gavage study by NTP (1986a), rats and mice had dose-related increases in forestomach hyperplasia, hyperkeratosis, inflammation or ulceration at $\geq$100 mg/kg, 5 days/week. The only nonneoplastic effect in rats treated with ethyl acrylate in the drinking water at concentrations up to 2000 ppm or dogs treated orally by capsule with up to ~931 ppm (TWA) was decreased body weight gain in high-dose female rats (Borzelleca et al., 1964).

In F344 rats given 0-110 mg/kg ethyl acrylate by gavage 5 times/week for 13 weeks, there were no treatment-related effects on body weight gain, longevity or clinical signs (NTP, 1986a). The only prominent histopathological change, occurring in the high-dose males, was an occasional reddened duodenum or pronounced stomach vasculature. Administration of up to 100 mg/kg ethyl acrylate to male and female B6C3F1 mice on the same treatment schedule had no effects on longevity, body weight gain or gross or microscopic histopathology (NTP, 1986a). Similar results were obtained by Treon et al. (1949) in two rabbits given 31.5 mg/kg ethyl acrylate orally, 5 times/week for 7 weeks. In a series of 14-day oral studies, the NTP (1986a) determined that gavage administration of 100 mg/kg/day ethyl acrylate in rats and 200 mg/kg/day ethyl acrylate in mice led to abdominal adhesions, thickened forestomach mucosa and nonulcerative inflammation. Administration of higher doses resulted in ulcers and more severe inflammation. Oral LD_{50} values ranging from 0.35-1.8 g/kg have been reported (Tanii and Hashimoto, 1982; Pozzani et al., 1949; Treon et al., 1949).

In the chronic inhalation study, nonneoplastic lesions of the nasal mucosa (e.g., hyperplasia, mineralization, inflammation, metaplasia) occurred in mice and rats at exposures ≥25 ppm (≥102 mg/m³), 6 hours/day, 5 days/week for up to 27 months (Miller et al., 1985). Exposure to 5 ppm, 6 hours/day, 5 days/week had no effect.

Inhalation exposure to lethal concentrations (1090 mg/m³, 7 hours/day for 28 days) of ethyl acrylate led to weight loss and severe signs of mucosal irritation in rats, guinea pigs, rabbits and in one monkey (Treon et al., 1949); these signs included conjunctivitis, lethargy and diarrhea. Examination of poisoned rats, guinea pigs and rabbits revealed multiorgan involvement and a variety of edematous and degenerative changes. These changes were found to be reversible in survivors that were sacrificed 2 months after termination of exposure. Exposure at 70 ppm (287 mg/m³) for 7 hours/day in rabbits, guinea pigs, rats and monkeys was without adverse effects (Pozzani et al., 1949; Treon et al., 1949). Lomonova and Klimova (1979) determined LC_{50}s of 16,200 and 7500 mg/m³ for unspecified durations for mice and rats, respectively.

Ethyl acrylate is a potent skin irritant (Pozzani et al., 1949; Treon et al., 1949) inducing erythema, edema, cellular necrosis and abscesses. Corneal necrosis after ocular application in rabbits was observed by Pozzani et al. (1949).

Since ethyl acrylate was carcinogenic in rats and mice, inducing squamous cell carcinomas or papillomas (or both) of the forestomach (NTP, 1986a), it is appropriate to derive a q_1^* for ethyl acrylate. According to U.S. EPA (1984) protocol, combined papilloma/carcinoma incidence should be considered for risk assessment. Since the highest tumor response was obtained in male rats, these data were selected as the most appropriate.

Data used in the calculation of the q_1^* are presented in Table 8-1. The transformed doses were calculated by multiplying the doses by 5 days/7 days and by 103 weeks/104 weeks. The unadjusted q_1^* of 8.86×10^{-3} $(mg/kg/day)^{-1}$ was calculated using the computerized multistage model developed by Howe and Crump (1982). The human q_1^* of 4.8×10^{-2} $(mg/kg/day)^{-1}$ was calculated by multiplying the unadjusted q_1^* by the cube root of the ratio of the reference human body weight (70 kg) to the weight of the male rats (0.44 kg, estimated from the growth curve in the study).

The human q_1^* can be used to determine the hazardous concentrations for increased lifetime cancer risks of 10^{-5}, 10^{-6} and 10^{-7} in drinking water if it is assumed that a 70 kg human drinks 2 ℓ of water daily (U.S. EPA, 1980). Division of each risk level by the human q_1^*, and multiplication of each result by 70 kg/2 ℓ/day, results in concentrations of 7.3×10^{-3}, 7.3×10^{-4} and 7.3×10^{-5} mg/ℓ, respectively, for the risk levels of 10^{-5}, 10^{-6} and 10^{-7}.

Values for q_1^* could also be derived for the incidences of squamous cell papilloma/carcinoma of the forestomach for female rats and male and female mice, but the resulting q_1^*s would be lower than that derived from the male rat data.

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: ethyl acrylate

Reference: NTP, 1986a

Species, strain, sex: rat, F344, M

Body weight: 0.44 kg (measured)

Length of exposure: (le) = 103 weeks

Length of experiment: (Le) = 104 weeks

Lifespan of animal: (L) = 104 weeks

Tumor site and type: forestomach, combined papilloma/carcinoma

Route, vehicle: oral gavage, corn oil

Experimental Doses or Exposures	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Tested
0 mg/kg, 5 days/week	0	1/50
100 mg/kg, 5 days/week	70.7	18/50
200 mg/kg, 5 days/week	141.5	36/50

Unadjusted q_1^* from study = 8.8632053×10^{-3} $(mg/kg/day)^{-1}$

Human q_1^* = 4.8025578×10^{-2} $(mg/kg/day)^{-1}$

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The subchronic and chronic toxicity of ethyl acrylate were discussed in Section 5.5. and a teratology study was discussed in Section 5.3. Since the teratology study was negative and since subchronic studies did not define effect levels lower than in the chronic studies, only the chronic studies are considered for the derivation of an RQ for ethyl acrylate. These chronic studies are summarized in Table 9-1. As seen from Table 9-1, the most severe effect was respiratory metaplasia in the chronic inhalation study by Miller et al. (1985). The lowest equivalent human dose at which this effect was observed was 1.8 mg/kg/day, which then multiplied by 70 kg, yields the MED of 126 mg/day, corresponding to an RV_d of 2.3. Metaplasia without evidence of organ dysfunction warrants an RV_e of 6. Multiplying the RV_d by the RV_e yields the CS of 13.8, which corresponds to an RQ of 1000 (Tables 9-2 and 9-3). Since the other effects were of lesser or equal severity and occurred at higher doses, there is no need to calculate CSs for these effects.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The carcinogenicity of ethyl acrylate was discussed in Section 5.1. The only positive carcinogenicity data for ethyl acrylate were described in an NTP (1986a) draft report. Fifty B6C3F1 mice/sex and 50 F344 rats/sex were given 0, 100 or 200 mg/kg ethyl acrylate by gavage, 5 times/week for 103 weeks. Comprehensive histopathology of sacrificed rats and mice revealed forestomach lesions (both neoplastic and nonneoplastic) as the only consistent dose-related effects. The increase in incidence of forestomach papillomas/carcinomas after treatment was most evident in male rats (see Table 5-1).

TABLE 9-1

Toxicity Summary for Ethyl Acrylate

Route	Species/ Strain	Sex	No. at Start	Average Weight[a] (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose[b] (mg/kg/day)	Response	Reference
Oral	rat/F344	M	50/group	0.44	corn oil gavage	99%	100 or 200 mg/kg, 5 days/week, 103 weeks	71.4, 142.9	13.2, 26.4	Dose-related forestomach lesions: inflammation, hyperplasia, hyperkeratosis	NTP, 1986a
Oral	rat/F344	F	50/group	0.24	corn oil	99%	100 or 200 mg/kg, 5 days/week, 103 weeks	71.4, 142.9	10.8, 21.5	Dose-related forestomach lesions: inflammation, hyperplasia, hyperkeratosis	NTP, 1986a
Oral	mouse/ B6C3F1	M	50/group	0.045	corn oil gavage	99%	100 or 200 mg/kg, 5 days/week, 103 weeks	71.4, 142.9	6.2, 12.3	Dose-related forestomach lesions: inflammation, epithelial hyperplasia and hyperkeratosis	NTP, 1986a
Oral	mouse/ B6C3F1	F	50/group	0.037	corn oil	99%	100 or 200 mg/kg, 5 days/week, 103 weeks	71.4, 142.9	5.8, 11.6	Dose-related forestomach lesions: hyperplasia, inflammation, hyperkeratosis	NTP, 1986a
Oral	rat/ Wistar	F	50	0.26	drinking water	NR	2000 ppm, 104 weeks	188.5[c]	29.2	Depression of body weight gain	Borzelleca et al., 1964
Oral	dog/ beagle	M,F	2/sex	9.1	dissolved in corn oil; administered in gelatin capsules	NR	933[d] ppm, 104 weeks	23.3[e]	11.8	Slight depression of body weight gain	Borzelleca et al., 1964

TABLE 9-1 (cont.)

Route	Species/ Strain	Sex	No. at Start	Average Weight[a] (kg)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose[b] (mg/kg/day)	Response	Reference
Inhalation	rat/F344	M,F	75/sex	0.27(M) 0.17(F)	vapor	>99.5%	25 ppm(102 mg/m³), 6 hours/day, 5 days/week, 116 weeks	12.6(M) 14.6(F)[f]	2.0(M,F)	Inhibition in body weight gain, olfactory mucosal hyperplasia, metaplasia, mineralization, increase in intraepithelial glands; adrenal medullary hyperplasia (males only)	Miller et al., 1985
Inhalation	mice/ B6C3F1	M,F	75/sex	0.015 (M,F)	vapor	>99.5%	25 ppm, (102 mg/m³), 6 hours/day, 5 days/week, 116 weeks	30.4[f]	1.8	Slight inhibition in body weight gain; submucosal hyperplasia, respiratory metaplasia	Miller et al., 1985

[a]Estimated from growth curves of body weight gain data

[b]Calculated by multiplying the animal dose by the cube root of the ratio of the animal body weight to the human body weight

[c]Calculated from water consumption and body weight data provided in the study

[d]TWA

[e]Assuming a dog consumes a daily amount of food equal to 2.5% of its body weight

[f]Calculated by multiplying 102 mg/m³ by 6 hours/24 hours, 5 days/7 days by the animal inhalation rate and dividing by the animal body weight. The inhalation rates were calculated according to formulas reccommended by U.S. EPA (1980).

NR = Not reported

TABLE 9-2

Inhalation Composite Score for Ethyl Acrylate Using the Mouse*

Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ
30.4	126	2.3	respiratory metaplasia	6	13.8	1000

*Source: Miller et al., 1985

TABLE 9-3

Ethyl Acrylate

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose*:	126 mg/day
Effect:	respiratory metaplasia with possible increased mortality
Reference:	Miller et al., 1985
RV_d:	2.3
RV_e:	6
Composite Score:	13.8
RQ:	1000

*Equivalent human dose

Three other chronic animal bioassays failed to find neoplastic changes after ethyl acrylate exposure. Borzelleca et al. (1964) treated rats with up to 2000 ppm ethyl acrylate in drinking water and dogs with the equivalent dietary concentration up to 933 ppm ethyl acrylate in gelatin capsules for 2 years. Although the extent of histological investigation was not described in detail (IARC, 1979a), Borzelleca et al. (1964) noted no increase in tumor frequency in either species. Groups of 60-75 F344 rats and 60-75 B6C3F1 mice of each sex were exposed to 0, 0, 25 or 75 ppm ethyl acrylate vapors, 6 hours/day, 5 days/week for up to 27 months (Miller et al., 1985). The only pathological changes consistently noted in sacrificed rats and mice were dose-related increases in nonneoplastic olfactory mucosal lesions. Incidences of thyroid follicular cell tumors were sporadically different (both higher and lower) from control incidences, possibly because of the high spontaneous occurrences of these tumors (NTP, 1986a; Miller et al. 1985). Finally, DePass et al. (1984) found no increases in ethyl acrylate-induced skin tumors in mice that were skin-painted 3 times/week for 2 years with 23 mg/mouse. Administration of 0.02 mg/mouse 3-methylcholanthrene, the positive control, on the same treatment schedule led to tumor development in 39/40 mice.

A causal relationship for increased incidences of colon and rectal cancer from occupational exposure to ethyl acrylate/methyl methacrylate was suggested in a retrospective epidemiology study (see Table 5-4); however, a clear causal relationship could not be established when further studies were considered (Rohm and Haas Co., 1981, 1984, 1986a,b; Mantel, 1986). Moreover, exposure to ethyl acrylate and methyl methacrylate could not be separated.

Ethyl acrylate was not mutagenic in prokaryotic reverse mutation assays (NTP, 1986a; Haworth et al., 1983; Waegemakers and Bensink, 1984). It did cause chromosomal aberrations in a CHL cell line (Ishidate et al., 1981) and a mouse micronucleus assay (Przykojewska et al., 1984) and also increased the number of forward mutations in a mouse lymphoma cell culture (Litton Bionetics, 1980). Most of the genotoxic changes observed in mammalian systems occured at cytolethal doses.

Based upon the data provided by the NTP (1986a), ethyl acrylate can be considered carcinogenic when given by gavage to experimental rodents. As discussed in Chapter 8, a q_1^* was calculated using the male rat data. Using the same data and the multistage model of Howe and Crump (1982), an unadjusted $1/ED_{10}$ of 3.99×10^{-2} $(mg/kg/day)^{-1}$ was calculated (Table 9-4). Adjustment of this value by the cube root of the human (assumed to be 70 kg) to the rat (0.44 kg) body weight ratio results in an F-factor of 2.16×10^{-1} $(mg/kg/day)^{-1}$.

According to U.S. EPA (1986b) guidelines, data from the NTP (1986a) study are sufficient in two species to consider ethyl acrylate a carcinogen. In the absence of adequate human data, ethyl acrylate should be considered a U.S. EPA Group B2 carcinogen. Because the F-factor is <1, ethyl acrylate is placed in Potency Group 3, which, along with a U.S. EPA classification of B2, gives ethyl acrylate a LOW hazard ranking under CERCLA.

TABLE 9-4

Derivation of Potency Factor (F) for Ethyl Acrylate

Reference:	NTP, 1986a		
Exposure route:	oral (gavage)		
Species:	rat		
Strain:	F344		
Sex:	male		
Vehicle or physical state:	corn oil		
Body weight:	0.44 kg		
Duration of treatment:	103 weeks		
Duration of study:	104 weeks		
Lifespan of animal:	104 weeks		
Target organ:	forestomach		
Tumor type:	papillomas/carcinomas		
Experimental doses/exposure (mg/kg):	0	100	200
Transformed doses (mg/kg/day):	0	70.7	141.5
Tumor incidence:	1/50	18/50	36/50
Unadjusted $1/ED_{10}$:	3.99049×10^{-2} (mg/kg/day)$^{-1}$		
Adjusted $1/ED_{10}$ (F factor):	2.162259×10^{-1} (mg/kg/day)$^{-1}$		

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in April, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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